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A TEXT-BOOK OF PHYSIOLOGY



# A TEXT-BOOK OF PHYSIOLOGY

BY

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## PREFACE

The subject of Physiology has grown to such large dimensions that it is impossible for a student to assimilate sufficient of it in the short time devoted to its study unless the material is presented to him in a systematic manner. This book is an attempt to present the elements of Physiology in an ordered sequence and the guiding principles have been as follows.

In its historical development Science has proceeded from a study of the form and movements of objects to the investigation of the less obvious and more complicated chemical interactions of the substances studied. During the life of an individual a similar mental development occurs leading him from a knowledge of the concrete to a consideration of the abstract. My aim has been to present the subject of Physiology on lines which will familiarize the student first of all with the gross mechanical processes in living structures and from such a basis lead on to the more intricate details of bodily activity. In order to keep the student in touch with the concrete basis of the subject frequent references are given to the practical applications of the information which is being imparted.

The first draft of the book was written whilst on active service in Egypt and in Palestine, and the development of it to its final form is the result of the experience gained by courses of lectures to medical students at St. Mary's Hospital Medical School and at the London Hospital Medical College. At the latter institution the practical courses are arranged to correspond to the course of lectures in the general development of the subject.

I have much pleasure in thanking those Authors and Publishers who have allowed me to make use of illustrations from various publications; the source of such illustrations is acknowledged under each figure. I am indebted to Dr. John Parkinson for the loan of a series of tracings from his own practice which are extremely valuable in illustrating certain facts of the circulation and respiration. Professor Sutherland Simpson submitted to me a series of

## PREFACE

photographs of thyroidectomized animals from which I was able to select an excellent illustration which shows the effect of thyroidectomy on growth and I wish to record my appreciation of his courtesy. I have special pleasure in thanking my friend and assistant Dr. W. A. M. Smart who has rendered invaluable help to me by discussion, criticism and suggestions during the preparation of the manuscript and by careful revision of the proofs.

H. E. ROAF.

LONDON HOSPITAL MEDICAL COLLEGE,

*August, 1924.*

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# A TEXT-BOOK OF PHYSIOLOGY

## INTRODUCTION

Physiology is the study of the activities of living organisms. In dealing with these activities we must investigate, not only the events themselves, but also the underlying processes associated with the events.

In order to simplify the description of the various activities of the body it is necessary to divide the description into compartments, but all the processes are interwoven and we must remember that the organism acts as a whole.

The activities of all living organisms seem to be directed ultimately towards the continuation of the species : this continuation depends upon two distinct processes which are the maintenance of individuals and the reproduction of similar or improved varieties of organisms. These two processes involve the same general principles of activity, e.g. oxidation and muscular movement, hence the starting point of Physiology should be an examination of the phenomena associated with the living organism.

The more obvious activities of living organisms are due to the transformation of energy potential and living cells may be regarded as transformers of energy potential. Thus an electric motor receives energy in the form of electrical potential and transforms it into kinetic energy and heat.

The living cell takes the place of the motor : it is supplied with energy potential in one form which it allows to run down to a lower level, and at the same time it increases the potential of another form of energy (Moore).

The above analogy suggests that we can deal with the activities of cells from a purely mechanical aspect. As this aspect is the simplest aspect to describe, it will form the first part of this book. Certain phenomena such as vision and hearing are left to a later section because their appreciation requires a knowledge of other branches of physiology.

## INTRODUCTION

The energy to be transformed by the living cell comes originally from the radiant energy of the sun. Chlorophyll-containing plants store the energy in the form of chemical compounds. This accumulation of energy is a problem belonging to the subjects of Biological Chemistry and Plant Physiology. The branch of Physiology which deals with animal organisms has to deal with the utilization by oxidation of the energy stored in chemical compounds.

The second part of this book deals with the chemical aspect of the subject, that is it deals with the way in which chemical compounds are taken into the body, the chemical changes that such compounds undergo in the body and the manner in which the products formed from them are removed from the body.

The purely physical and chemical aspects do not include the whole of physiology. There are processes which may be regarded as Biological : these are the means by which the energy transformations are controlled. It has been said that all the processes whereby the cells are controlled are also a matter of Physics and Chemistry. In the present state of our knowledge they must be given a place to themselves although physical and chemical concepts enter largely into the study of biological processes.

We must not forget that our physical and chemical concepts are merely a form of shorthand to describe phenomena appreciated by our senses. A mathematical formula expressing the relation of one event to another indicates that we can make quantitative measurements and show that they are related by a certain formula. The explanation of how a nerve cell responds to a stimulus fails to explain how this stimulation creates a sensation. It is not impossible, however, that ultimately we may be able to fit all biological activities into the concepts of a perfected Physics and Chemistry.

The third part of this book may therefore be described as the biological aspect of Physiology.

Finally we must consider the upkeep of the energy transformer and the production of new energy transformers. As pointed out above this seems to be the ultimate object of all the processes described in the preceding paragraphs, but there are certain phenomena which are more conveniently grouped under a separate heading. The processes of repair, growth and reproduction form the fourth part of this book.

The solution of the problems of Physiology would be much easier if we could take the living organisms to pieces and reconstruct them so as to act in the same way as they did before. But if we take a living organism to pieces it is dead and cannot be brought to life again. The extreme complexity of the subject of Physiology is due to the complicated methods that are necessary in order to investigate living organisms.

Obviously the ideal method would be some form of induction apparatus which could be tuned to respond to the activities of cells without injuring them. Failing such an ideal method we must make use of the best methods that are available. These methods depend upon a knowledge of other sciences and as the other sciences progress new methods and new hypotheses render possible further insight into cell activities.

In addition to a knowledge of Physics and Chemistry we require a knowledge of the structure of the organism that is being studied. The gross structure or Anatomy is essential for an understanding of the mechanical activities of the body. Knowledge of the finer or microscopic structure is necessary if we are to understand the intimate activities of the cells. In fact if we think of the finer and finer division of cells we finally reach the province of molecular Physics, and the interactions of chemical and physical forces which are the basis of the transformations of energy potential exhibited by the living cell.



## PART I

### MECHANICAL ASPECTS

From the mechanical point of view the most obvious functions of the body are those due to the activity of the skeletal muscles on the skeleton. Therefore the skeleton and the activity of its attached muscles are discussed first. Many of the phenomena associated with muscular activity can be studied by objective methods of such simplicity, that they are the easiest points for a beginner to understand. The more obscure processes underlying the contraction of muscle are deferred until the chemical aspect is being considered.

The action of the skeletal muscles in producing the rhythmical movements of respiration can be described, from the purely mechanical aspect.

The mechanical factors concerned with the action of pumps and the flow of liquids in tubes correspond to many of the problems of the circulation. Therefore the pulsation of arteries which is usually felt at the wrist as the "pulse" is a form of movement which will be included in this section.

## CHAPTER I

### THE SKELETON

In order to study the body as a machine we must pay some attention to the bony framework without which it would be a more or less shapeless mass. The bones serve a double purpose, namely protection and support.

**Protective Action of the Skeleton.** Protection of delicate structures by bone can be best illustrated by a few examples. The brain is contained in a box, the top and sides of which are formed of thin flat bones. The spinal cord is loosely suspended in the spinal canal. This protects the cord from injury from without.

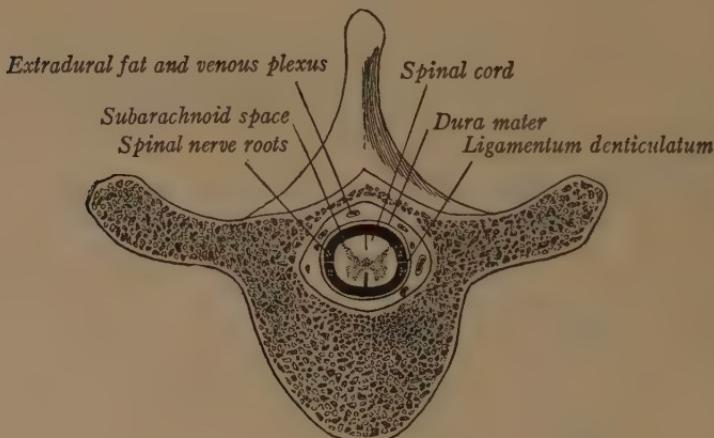


FIG. 1.—Diagram showing the Relation of the Spinal Cord to the Vertebral Column (Ranson's Anatomy of the Nervous System. W. B. Saunders Co.)

As shown in Fig. 1 the spinal cord is much smaller than the spinal canal so that movements of the vertebræ will not cause the cord to be squeezed by the bony margins of the vertebral canal.

The ribs with the structures uniting them form a protection to the heart and lungs. The main abdominal organs are either tucked up under the lower ribs, placed in the pelvis or wedged in the angle between the thick muscular masses forming the posterior wall of the abdomen. The exposed portion of the abdomen which is,

however, covered by firm muscular layers and a cushion of fat is occupied by the small intestine which by its softness and mobility is not easily injured.

Bone marrow is protected by the surrounding bone, and this arrangement at the same time makes a structure which has greater proportional strength than if the same amount of material formed a solid structure. The reduction in weight due to this arrangement is possibly of greater functional importance than the protection of the bone marrow.

**Supporting Action of Skeleton.** From the kinetic point of view the skeleton can be divided into a central axis with attached limbs.

The central axis is not a rigid system but has a flexibility which is useful in compensating and helping the movements of the limbs.

The limbs consist of a series of levers with joints between them. It is the action of these levers that causes progression and other movements.

The structure of the bones is not without interest. Like the stems of monocotyledonous plants the stiffer parts are arranged to give the greatest support for the least amount of material. This is the same principle that is used in engineering when the supporting girders are placed where they will most effectively bear the strain.

A solid structure subjected to a stress shows areas of compression and extension.

A beam supported at one end (Fig. 2) and weighted by a load in the direction of the arrow would be stretched on the upper surface and compressed on the lower surface. This has been indicated in the diagram by longer dashes above and shorter dashes below. Between the two areas there must be a narrow region where the material is neither stretched nor compressed : this is the neutral axis. Removal of the neutral axis makes no difference to the strength of the beam and close to the neutral axis the material is less strained than further from the axis. For this reason a smaller amount of material will be more effective if it is disposed where the main stretching and compressing forces are acting. Therefore a tube is more rigid than a rod of the same weight.

If we examine the strain lines in an irregular structure such as the head of the femur, we see that the downwards pressure on the head causes a compression on the inner side of the shaft and a

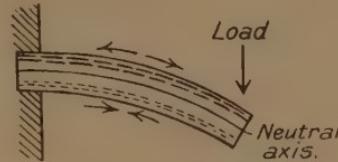


FIG. 2.—The Effect of a Load in Bending a Beam.

The upper surface is extended as shown by the two divergent arrows and by the longer dashes. The lower surface is compressed as shown by the two opposed arrows and the shorter dashes. The neutral axis is neither extended nor compressed.

stretching force on the outer side. The strain lines would run in the directions shown in Fig. 3.

One method by which strain lines can be studied is to use models made of transparent material like celluloid and examine them in polarized light. Regions of strain become visible by this method.

If the student examines a section through the head of the femur he will see that the bony lamellæ of the cancellous tissue show a pattern resembling that illustrated in the strain-line diagram, Fig. 3. The spaces between are filled with a lighter material (marrow). Thus the maximum strength is obtained with the minimum weight of material.

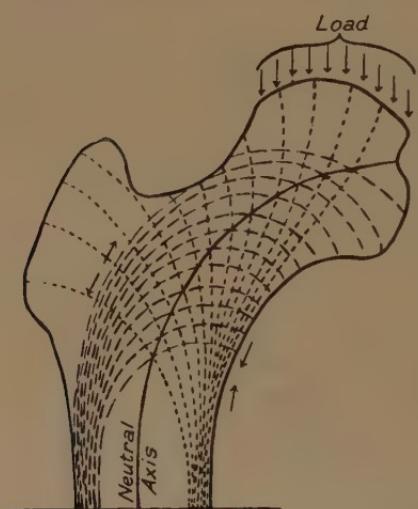


FIG. 3.—Lines of Stress due to a Load on the Head of the Femur.

As in Fig. 2, long dashes with divergent arrows indicate lines of extension and short dashes with opposing arrows indicate lines of compression. The neutral axis is also shown.

jarring, stretching or compressing of bone causes a further deposition of material where it is most required.

The structure of a long bone consists of a hollow shaft with a wall of dense bone and expanded ends formed of a honeycomb network of delicate bony trabeculae. The wide ends form broad surfaces of contact with neighbouring bones. The crushing force of the weight of the body is distributed in this way over a wide area and there is sufficient room for the bones to slide over each other during movement. The hollow shaft and the arrangement of the cancellous tissue seems designed in agreement with the requirements of the forces to which they are subjected: that is the bone corresponds to the strain lines as shown in Fig. 3.

Not only does the natural structure show this arrangement of bony material to give the maximum strength, but after a fracture when the bone has united in a wrong position it is known that the bone is gradually absorbed and remodelled so that it is best able to bear the strain placed upon it. A similar process of adaptation occurs in bone which has become bent during an attack of rickets: the concave side is buttressed by dense hard bone.

This is a most remarkable phenomenon and indicates the kind of difference often seen between living and inanimate structures. The

Between the bones are buffers of cartilage to minimize the effect of jarring at the joint surfaces.

The bones are united by connective tissue which limits the extent of movement of the joint surfaces. An important factor in the stability of the joint is the elastic tension of the muscles which by their pull hold the joint surfaces in apposition.

**Movements of Bones.** The shape of the joint surfaces has a marked effect on the degrees of freedom shown at the joints. Physically we recognize six degrees of freedom ; three of movement in three planes at right angles to each other and three of rotation. Joint surfaces are not simple physical problems because both rotation and translation occur, but the total effect of joint movement is rotation about a point situated in or near the joint cavity.

The greatest number of degrees of movement are found in ball and socket joints, such as the hip and shoulder, in which three rotations are possible. The next most mobile type of joint is the saddle-shaped joints, such as the metacarpo-phalangeal joints, which allow two degrees of rotation. The third type of joint is the hinge joint, such as the knee or elbow, which allows only one degree of rotation. Finally there is a form of union which is not a true joint : this is where two bones are united by cartilage, such as the junction of the ribs with the sternum, where a certain amount of movement is possible by deformation of the cartilage.

The extreme mobility of the elbow, wrist, ankle, neck, etc., is due to there being more than one joint surface, so that quite complicated movements can occur by the combination of two or more simpler ones.

**The Action of Bones as Levers.** The mechanical properties of levers must be described in order to explain how the movements of the body are executed.

Every lever has three salient points and according to the arrangement of these points three varieties of levers are described. The first point is the fulcrum or support, the second is the resistance and the third is the force or power. The three varieties of lever are illustrated in Fig. 4.

1. *A lever of the first order* is one in which the fulcrum is situated between the resistance and the power. The example given is the balancing of the head on the atlas vertebra. The fulcrum is the joint between the atlas and occipital bone. The resistance is the excess weight of the front of the head tending to cause it to fall forwards. The power is the muscles attached to the occipital protuberance. If the resistance and power are balanced no movement takes place and the head remains in its upright position.

2. *A lever of the second order* is one in which the fulcrum is at one end and the power at the other end. In the example given the

fulcrum is at the base of the toes where the foot rests upon the ground. The power is the muscles attached to the heel and the resistance is the pressure at the ankle joint.

If the distance of the axis of the ankle joint from the point of contact with the ground is three times the distance of the axis of the joint from the attachment of the muscles we can calculate the forces at the various points as follows.

When an individual is standing on the toes of one foot the pressure on the ground is his weight. If this is 70 kilos the pull at the heel necessary to balance this must be 210 kilos. The turning moments about the centre of rotation must be equal and the turning moment about a point is the force multiplied by its vertical distance from the axis of rotation.

As the ankle joint balances these two pulls, the total pressure in the joint must be equal to 280 kilos.

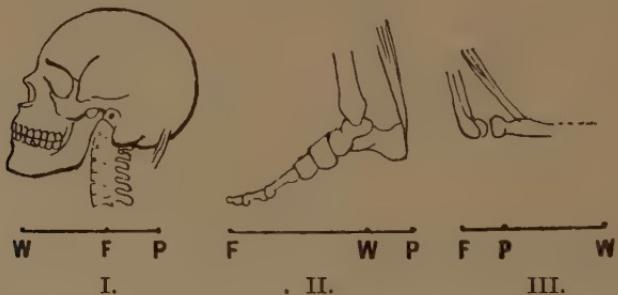


FIG. 4.—Diagram of Three Kinds of Lever Action (Leonard Hill).

F = fulcrum, P = power, W = weight.

- I. Lever of the first order. The head is tilted back by the muscles of the neck.
- II. Lever of the second order. The toes rest on the ground and the weight of the body is raised by contraction of the muscles of the calf.
- III. Lever of the third order. The forearm is lifted by the contraction of the biceps muscle.

*3. A lever of the third order* is one in which the fulcrum is at one end and the resistance at the other, the power lying in between. The example given shows how leverage may be used to increase speed of movement. The distance of the mid point of the hand is about six times as far from the axis of the joint as is the insertion of the biceps. Therefore when the insertion of the muscle moves one inch the hand will move six inches, thus the speed of the movement of the hand will be six times the rate of the shortening of the muscle.

The effect of this increase in speed is manifest in the delivery of a cricket ball in bowling. If the length is increased by means of a stick still greater speed is developed, as in striking a golf ball with a driver in which the wrists, elbows, shoulders and spinal column all act together to produce a high rate of speed when the club hits

the ball. The wrists are especially important because a slight angular rotation of them causes a long arc to be traced by the head of the club.

Another mechanical result of the limbs acting as levers is that they behave as compound pendulums. The swing of a limb is most easy when its rate of swing is that of a similar pendulum. The swing of a pendulum is determined by the distance of the centre of gravity from the point of support. It follows from this that the easiest rate at which a limb will swing is that which corresponds to its period of oscillation. A short leg will tend to produce a short quick step and a long one a long, slow pace. By attempting to alter the natural pace more muscular effort is involved : this produces fatigue and it is one reason why troops should be selected according to their height or what would be better still, the length and swing of their legs..

One can prove this for oneself by wearing a pair of heavy boots which by their weight make the centre of gravity of the leg further from the hip. Compare the length and rate of pace walking down a smooth gentle slope in light slippers and when wearing heavy marching boots.

**Motion Studies.** That the inertia of the moving parts is of great importance is shown by the study of movement in industrial processes. By altering manipulations it is possible to increase the output with a decrease in the fatigue of the worker. One method of studying such movements is to attach a light to one of the moving parts and to photograph the light. The record shows a continuous line representing the path traced by the moving part.

### Centre of Gravity

Later on we shall have to study the manner in which the equilibrium of the body is maintained, hence we must understand the problem to be studied. When an object is suspended it hangs so that its centre of gravity is vertically below the point of support. This is the condition of stable equilibrium. If, on the other hand, an object is stood upright it will remain in that position only if its centre of gravity is vertically over its point of support. This is an example of unstable equilibrium.

In balancing a rod on one finger the rod is maintained upright by moving the supporting finger. When the rod begins to fall the finger is moved in the direction to which the rod inclines until the finger is under the centre of gravity of the rod. As a rule the movement over-corrects the tendency to fall and balancing consists in a series of movements always attempting to keep the supporting finger under the centre of gravity of the rod.

Our balance is maintained in a slightly different manner. With the feet fixed in position there is no movement of the base of support. The body is kept upright by slight muscular movements. When the centre of gravity tends to move beyond the base of support muscular contraction pulls it back. Therefore equilibrium requires a delicate adjustment whereby the various parts of the body are so adjusted that the centre of gravity is maintained over the base of support. This is a much more complicated problem than balancing a rod.

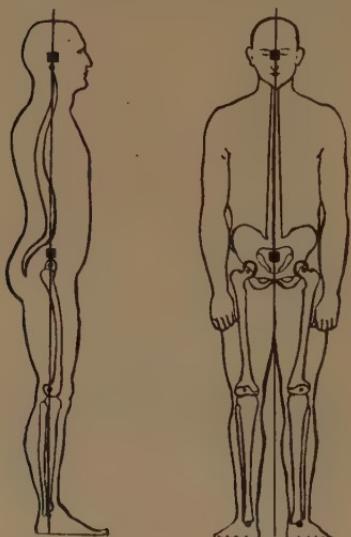


FIG. 5.—Showing the Position of the Centre of Gravity of the whole Body and of the Head (■) and also of the Centres of Rotation of the chief joints (●) in reference to three co-ordinate planes (Braune and Fischer).

(From Haycraft in Schafer's *Text Book of Physiology*, Oxford Medical Publications.)

are placed wide apart, and when resisting a force from the front one foot is placed in front of the other. The centre of gravity in the upright position is nearly at the level of the anterior superior iliac spines and midway between them. It need not, however, be in the body because on leaning forwards or backwards the centre of gravity is outside the body.

The position which can be most easily maintained is that in which there is least muscular strain. This can be worked out for each joint by finding the centre of gravity of the parts above that joint and placing the centre of gravity as nearly as possible over the

In order to keep the centre of gravity over the two feet it is necessary that the tibia be balanced on the ankle joint, that the femur be balanced on the knee joint and the pelvis balanced on the hip joint. Imagine the skill required to balance three rods in a vertical row. The base consists of the two feet, each of which has three points of contact with the ground, namely the heel, the base of the hallux and varying proportions of the outer digits. Thus each foot is a tripod and the two feet present six points of support.

Fig. 5 shows the position of the centre of gravity of the whole body and of the head. The axis of rotation of some of the joints is also shown.

The extent of the base may be varied by placing the feet in different positions. When resisting a push from the side the feet



FIG. 6.—Shows the Area of Underpropping and the Plumb of the Centre of Gravity *g*.

(1) At attention. (2) In an erect and easy attitude. (3) When resisting a force applied from the left. (4) When resisting a force applied from the front, as in boxing. (From Haycraft in Schafer's *Text Book of Physiology*, Oxford Medical Publications.)

axis of the joint. The further the centre of gravity is from the perpendicular the greater the muscular effort in maintaining the

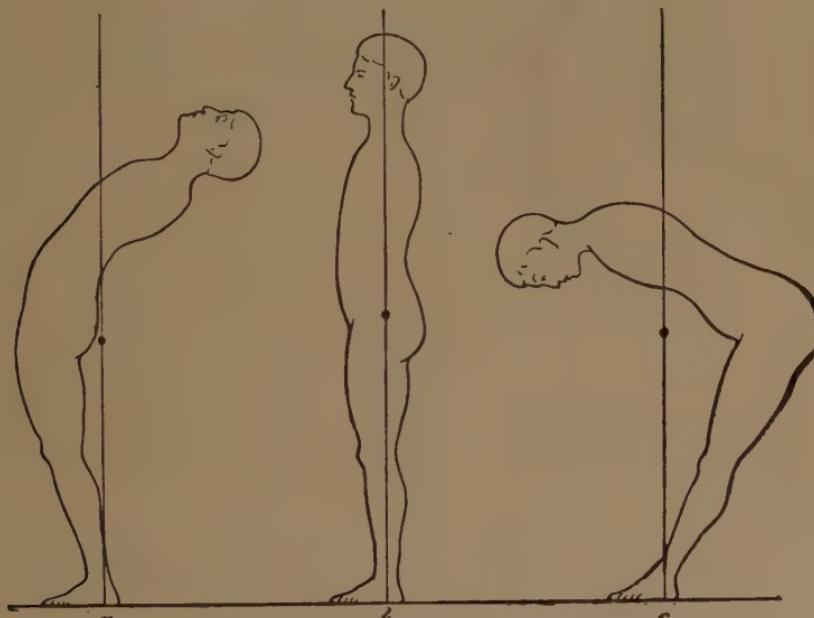


FIG. 7.—Position of Centre of Gravity indicated by a dot.

In *a* and *c* the centre of gravity lies outside the body. (From Haycraft in Schafer's *Text Book of Physiology*, Oxford Medical Publications.)

posture. In reality the easiest way to stand is that which allows slight variations in position as in "standing at ease." As we shall see in studying muscles fatigue is more rapidly produced by continuous contraction than by slight variations in contraction.

The necessity of maintaining the centre of gravity over the base of support is best seen by standing on one foot. On shifting from both feet to one foot the hips shift towards that side on which the foot is being used, and compensatory movements of the shoulders

and other parts occur. If the hips are prevented from moving outwards it is impossible to stand on one foot. Thus it is impossible to stand on one foot placed against the base of a vertical wall.

*Walking.* When we pass from the static condition of standing to study movements we must remember the effect of inertia. A moving object tends to continue in a straight line, hence it may be possible for the centre of gravity to be beyond the base of support when the body is in movement. In order to show the effect of this inertia we shall first describe a slow movement such as walking, and then show the difference between it and a rapid movement such as running.

FIG. 8.—Man dressed to show Movements of the Body during Progression.

The axes of the rotation of the joints and the axes of the limbs are represented in white on a dark background. (After Marey, from Haycraft in Schaffer's *Text Book of Physiology*, Oxford Medical Publications.)

Walking may be described as falling forward followed by recovery. It has been extensively studied by photography and the experiments in the study of movements led to the invention of the kinematograph.

One method of study is to clothe a man in black, mark the direction of his limb bones by white lines and the axis of the joints by white dots. A series of photographs is taken on the same plate and the record shows the successive positions of the body and limbs during walking. This record shows the movements of only one



side but the other side would show a similar series of movements alternating with those on the side shown.

From the standing position walking is accomplished by leaning forward; when the body commences to fall forwards one foot is raised, swung forward and its heel placed on the ground. The body falls forwards and towards that side on which the foot is raised. When the heel is in contact with the ground that leg is straightened and the weight is moved over this foot by the push of the toes of the other foot. The second foot is now raised clear of the ground by flexion of the knee and lifting of the toes. This foot is in its turn swung forwards by a pendular action aided by muscular contraction until it reaches a position where the heel is placed on the



FIG. 9.—Chronophotograph of a Man's Movements when Walking.

Read from left to right. (After Marey, from Haycraft in Schafer's *Text Book of Physiology*, Oxford Medical Publications.)

ground by the extension of the knee. This alternate swing of the legs continues at each step.

During these movements of the legs the hips show a double sinuous curve. When the body is falling forward the hip moves in the arc of a circle of which the centre is the ankle joint, and the radius is the leg and thigh. Whilst the body is being pushed over the other leg the hips must be rising in the arc of a circle formed by that leg. Thus for each complete cycle of one leg, two up and down movements of the hip occur, corresponding to the movements of each leg.

With each step there is also a side to side movement as the body sways in order to keep the centre of gravity near the inner border of each foot in turn. Numerous compensatory movements of other parts of the body occur.

Owing to the shortness of the ilio-femoral ligament in the female her leg cannot be swung backwards so far as in the male. In order to take a long stride she must twist her pelvis on the vertebral column. Her gait is characterized by a greater degree of rotation of the hips than occurs in the male. It is an interesting speculation as to whether this shortness of ilio-femoral ligament and twisting of the pelvis may be an adaptation to compensate for the width of her pelvis. By twisting her pelvis her centre of gravity can be more readily kept near the inner margin of each foot in turn, otherwise she would be forced to make greater side to side movements during walking.

**Running.** This differs from walking partly because of the greater speed. It consists of a series of leaps as both feet are off the ground at the same time. Owing to the greater speed the inertia of the body keeps it more nearly in a straight line and undulations of the hips are less marked.

**Joints.** To prevent injury from jarring of the bones the articular surfaces are covered by cartilage. Sometimes special pads of cartilage are present, as in the knee joint, and in the vertebral column there are thick fibro-cartilaginous discs between the bones. Another way in which joints prevent shocks is by allowing movement to occur. This is exemplified by alighting from a jump with bent legs. The movement is stopped gradually by the tension of the muscles attached to the bones forming the joint. The joint bends and the kinetic energy is more gradually absorbed just as buffers decrease the shocks when railway carriages are rapidly stopped.

The joint surfaces are smooth and there is a lubricating liquid in the cavity. Wherever friction occurs we find a similar arrangement. Serous cavities and tendon sheaths are lined by flat pavement cells making a smooth surface. A small quantity of liquid between the surfaces allows them to slide easily over one another.

The above brief outline of some of the mechanical factors concerned in bodily movement is an indication of some of the problems to be studied later.

A detailed study of joints and the lever action of bones is essential for the subject of Orthopædics.

**NOTE.**—For further information the student should consult J. B. Haycraft, *Animal Mechanics; Text Book of Physiology*, edited by E. A. Schafer, 1898, vol. ii, pp. 228–273 (Oxford Medical Publications); and G. Weiss, *Die Chronophotographie Ergebnisse der Physiologie*, 1906, vol. v, pp. 289–318.

## CHAPTER II

### ACTION OF MUSCLES

In the preceding chapter we considered briefly the framework of the body and the laws which regulate its movements ; now we must proceed to examine the power that produces these movements. The movements are brought about by shortening of fleshy bonds called muscles.

**Varieties of Muscle Tissue.** There are three varieties of tissue which possess the property of increasing the tension between two points. If these points are not fixed the distance between them is decreased, i.e. the muscle shortens. The three varieties are called skeletal, cross striated or voluntary muscle ; involuntary or smooth muscle ; and cardiac muscle. They differ in structure and in their physiological properties : in this chapter the behaviour of striated muscle will be described with occasional references to the other varieties. The properties of the other muscles will be described in later chapters.

**Cross Striated Muscle.** These muscles when magnified are seen to be composed of fibres which show a transverse striation. Striated muscle is probably the best name for them as they are not always attached to the skeleton, nor are they always under voluntary control.

They form the only means by which the skeleton is moved, hence they are of paramount importance to the individual, since they furnish the means by which he executes all his wishes. They are also of importance for the two following reasons.

1. Their bulk represents about 40 per cent. of the total weight of the body and they furnish the greater proportion of the chemical changes, such as oxidation, which occur in the body. Mere size, however, is not the only criterion of importance because, as we shall see later, there are small organs, less than one five-thousandth of the body weight, removal of which may cause death.

2. They possess a definite form of activity which can be easily studied, especially in cold-blooded animals such as amphibia. The chemical changes which take place during muscle activity are probably similar to the chemical changes which take place in other tissues, thus they form a basis from which to discuss the

changes which take place in other tissues during their activity.

A muscle consists of a fleshy central portion with two tendinous ends. The ends are attached to bones ; the one which is attached to the bone nearest to the central axis of the body is known as the fixed end or origin, whilst the end which is attached to the bone furthest away from the central axis is the movable end or insertion ; i.e. the more peripheral bone is moved relatively to the more central bone, although both may participate at the same time in a movement brought about by muscles still nearer to the central axis.

The fundamental activity of muscle is to produce an increased tension between the two attached ends. If the joint (or joints) over which the muscle extends is free to move, the muscle shortens and the bones move relatively to each other. This shortening is usually spoken of as contraction.

Normally a muscle becomes active in response to an impulse from the central nervous system. This impulse reaches the muscle through a motor nerve and activity can be produced by artificial excitation of the nerve. As we are considering the purely mechanical side of activity it is sufficient to study here the manner in which activity may be artificially produced and to show that muscle may possess activity independently of any impulse reaching it by a nerve.

**Forms of Stimuli.** A tissue is made active by the action of an external agent called a stimulus : the response of the tissue to the stimulus shows that it possesses excitability or irritability.

Various forms of stimuli can be used to produce activity in a nerve, the indicator for the activity being in the present case the contraction of muscle.

If the nerve of a muscle-nerve preparation is acted on mechanically by tying a ligature round it or by tapping it with a light hammer the muscle contracts.

If crystals of salt or strong glycerine is applied to the nerve the muscle shows irregular contractions.

If a hot wire is applied to a nerve the muscle likewise contracts.

These forms of stimuli are difficult to regulate and usually injure the nerve so that a second stimulus at the same place or further from the muscle fails to produce any response in the muscle.

The stimuli which are most often used are electrical. These are more convenient than the others because they can be accurately graduated, the nerve is not noticeably injured and stimuli repeated at the same place produce activity of the muscles. The electrical stimuli may take the form of alterations in strength of a continuous current or the current of short duration from the secondary coil of an induction coil.

The methods of electrical stimulation must be studied in a

practical course. A brief description of some of the electrical apparatus will be found in the Appendix.

**Independent Excitability of Muscle.** Nerves are distributed to muscle in the form of fine branches running between the contractile tissue; thus direct stimulation of muscle may be effective by stimulation of these branches. That muscle possesses excitability independently of nerve can be shown by three simple experiments and by conclusions drawn from the study of the response of muscle and nerve to special stimuli (see page 308). The three former will be given here and the last deferred until we are in a position to study the nature of electrical stimulation.

(1) By the action of curari the conduction between nerve and muscle is interrupted. The following experiment makes use of this interruption to show that muscle possesses independent irritability. Two muscle-nerve preparations from a frog are placed in two watch glasses so that the nerve of one is in the watch glass with the muscle of the other, and vice-versa. Into one watch glass is poured Ringer solution (see p. 152) and into the other Ringer solution containing dilute curari. After half an hour the two preparations are stimulated. First the nerve which has been in curari is stimulated and it is seen that the muscle contracts, showing that the curari does not affect nerve fibres. Next the nerve which was not in curari is stimulated and the muscle which was in curari fails to contract, showing that the curari prevents the nerve impulse from causing the muscle to contract. But if that muscle is now stimulated it contracts, showing that some substance in the muscle responds to electrical stimulation, although the nerve fibres cannot pass a stimulus on to the muscle (Claude Bernard).

(2) A second method which shows that muscle can be excited independently of nerve is by chemical stimulation. Direct application of dilute acid (0.5 per cent. HCl) or dilute ammonia (a trace only) causes contraction of muscle, whilst to stimulate nerve requires strong acid (9 per cent. HCl), and even strong ammonia fails to cause contraction of muscle when applied to nerve (Kühne).

(3) A third method depends upon the existence of parts of muscle which are free from nerve fibres. Careful microscopical examination of the frog's sartorius shows that nerve fibres ramify in its central portion, but they are not found in the last four or six millimetres of the pelvic end. Thus glycerol causes contraction of muscle when applied to its nerve but does not cause contraction of the nerve-free end of the sartorius. Direct stimulation of the nerve-free end of the sartorius by carefully regulated electrical stimuli will cause contraction of the muscle, thus indicating that muscle fibres free from nerve fibres can be electrically stimulated

(Kühne). This method of proof is not so direct and convincing as the first two.

Having established that muscle can be stimulated independently of the nerve we may now study the phenomena of contraction, using stimuli applied either directly to the muscle or indirectly through the nerve, whichever is more convenient for the experiment.

**Isotonic and Isometric Contraction.** The fundamental phenomenon of contraction is that there is an increased tension between the two ends of the muscle. Two distinct methods can be used to demonstrate this tension. In the first we can suspend the muscle vertically and attach a weight to it. An increase in tension will cause the muscle to shorten and the weight will be

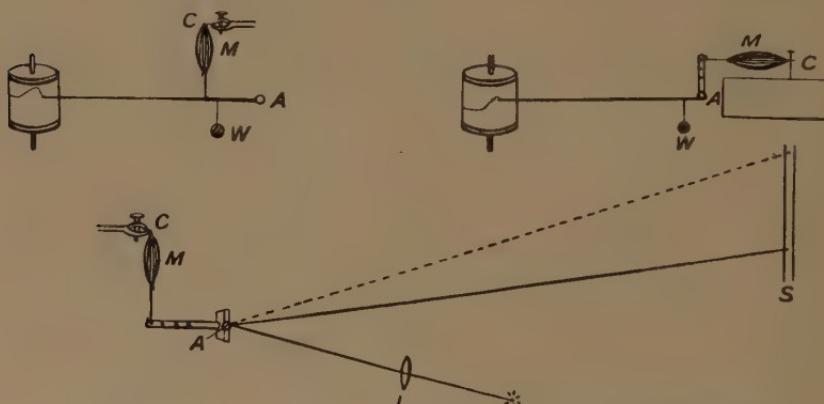


FIG. 10.—Diagram showing various Methods for recording Muscle Contractions.

Top left: Straight lever with direct lifting of weight. Top right: L-shaped lever. Lower Fig.: Optical recording. The light is projected on a small mirror so that a spot of light is focussed by lens *L* on the camera slit *S*. Contraction of the muscle *M* causes the image of the light to move from the position shown by the interrupted line to that shown by the continuous line.

If, instead of an axis *A* and weight *W*, the levers are mounted on a fixed wire, movement can take place only by twisting the wire and the levers become isometric, the length of the muscle from the clamp *C* to the lever remaining practically unaltered.

lifted. As the tension on the muscle is the same throughout, this is called isotonic contraction. The other method is to suspend the muscle to two fixed points. In this condition the muscle cannot shorten and any change will be an increased pull on the points of support. As the length remains unchanged this is called isometric contraction.

When we attempt to record the contraction of muscle we cannot always realize these ideal conditions, but we can obtain conditions where the contraction is almost entirely isotonic or isometric.

In order to make a record of an isotonic contraction either a straight or bent lever may be used. Two forms of such recording apparatus are shown in Fig. 10, in which a muscle is seen lifting a weight. The levers are pivoted on an axle at *A*.

This is almost isotonic as the muscle lifts the weight of the lever plus the extra weight ( $W$ ) suspended from the lever. As the muscle shortens, the lever describes an arc of a circle, and therefore the tension on the muscle will vary slightly because of the change in the moments of the forces about the axis. In the case of the weight its pull is exerted vertically downwards. As shown in Fig. 11, when the lever has risen from  $AB$  to the position  $AC$  the turning moment will now be proportional to  $AD$ . Therefore the tension due to the weight will be less in the ratio of  $AB : AD$ . This has been shown

on an exaggerated scale in order to show how the tension alters as the inclination of the lever changes. Similar considerations apply to the pull of the muscle. The direction of the pull alters, and its vertical component round the axis of rotation will change.

Isometric contraction is recorded by causing the muscle to pull against a stiff spring. The muscle must shorten slightly, but the main effect is an increase in tension as the spring is bent. A convenient form of spring is to replace the axle of the lever by a piece

FIG. 11.—Diagram to show Variation in Tension due to the Weight with change of Angle of the Lever.

$$AC = AB, \quad AD = AC \cos \phi = AB \cos \phi. \quad \therefore \text{Moment of weight about } A = W \times AB \text{ and } W \times AB \cos \phi \text{ when the lever is horizontal and raised through angle } \phi \text{ respectively.}$$

of wire to which the lever is rigidly attached. The two ends of the wire are clamped, therefore pulling on the lever by the muscle will cause a twisting of the wire.

Another method for recording isometric contraction is to use a flat spring with a knife edge at its extreme end. The knife edge supports a light lever close to the axis of the lever, therefore a slight movement of the spring will be highly magnified by the lever.

**Inertia of Moving Parts and Recording Methods to Minimize Inertia.** In all instruments where levers are used the weight of the lever introduces a source of error. The inertia of the lever delays the start of the movement, and when the lever is in motion it continues the motion after the force acting on it has ceased.

When the rate of movement is slow and the frequency of the lever is great the error is less, nevertheless there may be vibrations due to the lever superimposed on the movements that are being recorded. For simple direct records levers are more convenient, but where accurate records of time relations are required photographic records are better. Photographic records may be made by allowing the shadow of the moving object to fall directly on the moving photographic plate (see Fig. 58, p. 78), or a magnified image may be recorded (see p. 40).



A small mirror at the axis of rotation and mounted on a wire clamped at its two ends, makes an isometric lever of high frequency. Slight torsion of the wire causes a slight tilting of the mirror. An image of a light is thrown on a camera slit. As shown in Fig. 10 contraction of the muscle causes a movement of the image downwards from the position shown by the dotted line to that shown by the continuous line. In this way magnification can be obtained without adding to the weight of the moving parts.

The isotonic and isometric forms of contraction occur frequently in muscular activity. As will be shown later the heart reveals both isotonic and isometric phases during its contraction.

**Muscle Tone.** A resting muscle is an extensile and resilent structure. This is a point of more than academic interest because the muscles in the body are slightly extended. If a muscle is freed from its attachments it shortens, showing that it had been stretched. Because of this stretching a wound across muscle fibres or tendons gapes more than one lengthwise to the fibres. This slight tension of muscle is known as tone and the condition of tone must be studied later on. Tone can be abolished during deep anaesthesia or when the nerve is cut so that the muscle is removed from the influence of the central nervous system.

**Pseudo-Elasticity of Muscle.** To study the extensibility of muscle we can measure its length when different weights are suspended from it. If we compare the results with the extension of a metallic spring we find the following differences.

The extension of an elastic band, within the limits of its elasticity, is proportional to the weight suspended on it. Thus if a record can be made by hanging weights on a lever such as one of those shown at the upper part of Fig. 10. The muscle is replaced by an elastic band and the recording surface is moved onwards equal distances for equal increments of weight. A record made, for instance, by the successive addition of ten gram weights with the drum moved one centimetre after the addition of each weight, will show the appearance of a regular flight of steps. Fig. 12 shows the result of the extension of an elastic band.

On the other hand muscle does not extend in proportion to the weight added, but the extension with greater weights is less in proportion. The curved line in Fig. 12 shows very clearly this lack of proportional extension.

During this experiment it will be noted that the muscle extends more slowly than the elastic band, and the weight must be left on long enough for the muscle to reach a condition of equilibrium. This delay in reaching the equilibrium condition (hysteresis) is probably due to mass movements of liquid in the muscle. When the weights are removed the spring shortens rapidly whilst the



FIG. 12.—Elasticity of Muscle contrasted with that of an Elastic Band.

The latter shows equal increments of length for equal additional weights, the former extends less, for equal increments, when the total weight is great than when the total weight is small. (From Waller's *Human Physiology*, Longmans, Green & Co.)

muscle takes a considerably longer time to reach its initial length. Muscle activity causes a change in tension, that is to say that the relation between length and tension is altered. Thus if we measure the extensibility of contracted muscle we find that it is different from the extensibility of resting muscle. The experiment is carried out in the same way as in the case of resting muscle. The various weights are put on the muscle which is caused to contract until the weight is lifted as far as the muscle can do so. By plotting the lengths of the contracted muscle unloaded and with varying loads the extension of the contracted muscle can be measured as shown in Fig. 13.

The extensibility of the contracted muscle is greater than that of the uncontracted muscle. Thus, for any given load, the distance between the lines



FIG. 13.—Comparative Extensibility of Resting and Contracted Gastrocnemius.

Temp., 12° C.; magnification 5. Figures represent actual weights in grms. R is the "resting" and C the "contracted" abscissa line (A. P. Beddard).

representing the length of unloaded contracted muscle and the loaded contracted muscle is always greater than the distance between the length of the unloaded resting muscle and the loaded resting muscle. If the two curves shown in Fig. 13 are continued by using still greater weights, they will meet and their prolongations will cross; this is called *Weber's Paradox*, and it represents the absolute force of the muscle as it is the weight which the muscle just fails to lift.

The explanation of this phenomenon is probably to be found in the presence of connective and other non-contractile tissues in a muscle. As the muscle is extended, a greater proportion of the weight is borne by these structures. When the weight is too great to be lifted the increased tension in muscle merely relieves some of the tension which was exercised on the non-contractile elements.

**Responses of Muscle to Stimuli of Different Strengths.** The response of a muscle to weak stimuli varies with the strength of the stimulus.



FIG. 14.—Heights of Contraction of a Muscle with different Strengths of Stimuli.

M marks the make and B the break of the primary circuit. The numbers refer to the distances in cms. of the secondary from the primary coil (A. P. Beddoe).

If we use a single shock (either make or break) from an induction coil, and the secondary coil is well separated from the primary coil we find a limit beyond which the stimulus is ineffective on the muscle. As the secondary coil is moved closer to the primary coil we reach a position where the shock is just sufficient to produce a minimal response. This is called the limen or threshold and stimuli below this are called *subliminal*. As the coils are brought closer together the response to the stimulus becomes greater up to a certain point beyond which increase in strength of the stimulus produces no greater effect. We speak of the least response as minimal, the greatest response as maximal, and the intermediate ones as submaximal. As will be shown later the difference in the strength of contraction is due to the stronger stimulus causing more fibres to contract and not to varying contraction of the same fibres.

In this experiment either the make or the break of the current must be used throughout because physically the break shock of the induction coil is always stronger than the make shock.

In experiments shown in Fig. 14 the lever attached to the muscle has been made to write on a stationary surface. The actual shortening of the muscle can be measured by dividing the height of the record by the ratio, total length of the lever divided by the distance of attachment of the muscle from the axis.

#### GRAPHIC RECORDS AND ANALYSIS OF MUSCLE CURVES

If we wish to study the muscle phenomena further the recording surface is made to move at right angles to the direction of movement of the lever. By means of a time measurer, which for rapid speeds is usually a writing point attached to a vibrating tuning fork, the rate of movement can be measured. The to-and-fro vibration of the tuning fork is drawn out into a sine curve as the surface moves at right angles to the vibrating point. In the same way the up-and-down movement of the muscle lever is drawn out into a curve. Maximal stimuli must be used for the following experiments.



FIG. 15.—A Single Contraction of Frog's Gastrocnemius (Flack and Hill).

The latent period, period of contraction and period of relaxation, are demarcated by upright lines. Read from left to right. Time marking in  $\frac{1}{100}$  secs.

If the exact point where the stimulus is given is marked one obtains the curve shown in Fig. 15.

The first upright line shows the place on the moving surface at which the stimulus is sent into the preparation. The lever commences to rise at the second upright line, and it rises until it reaches its maximum, after which it falls again. The final length is on or very close to the original base line. If the mechanical factors have been so arranged that the inertia of the lever has been excluded the curve represents changes in length of the muscle. A similar record by an isometric lever would show changes in tension produced by the contraction of the muscle.

From the first to the second line there is apparently no change in the muscle. This is called the *latent period*, and it is occupied by the changes in the muscle preparatory to contraction. The length of time occupied by these changes depends partly on the

place of stimulation. If the nerve is stimulated we can show that the further from the muscle that it is stimulated the longer the latent period. This indicates that one factor in the latent period is the time required for the impulse to travel along the nerve. Other factors are the passage of the impulse from the nerve to the muscle; the changes in the muscle which produce an increase in tension and change in length; and in many cases the inertia of the moving system may be responsible for part of the delay.

From the second to the third lines the muscle is shortening (or increasing in tension) and if inertia of the lever system be excluded the curve represents the extent of shortening and the time occupied in accomplishing the shortening.

The means of analyzing movements by recording them on a

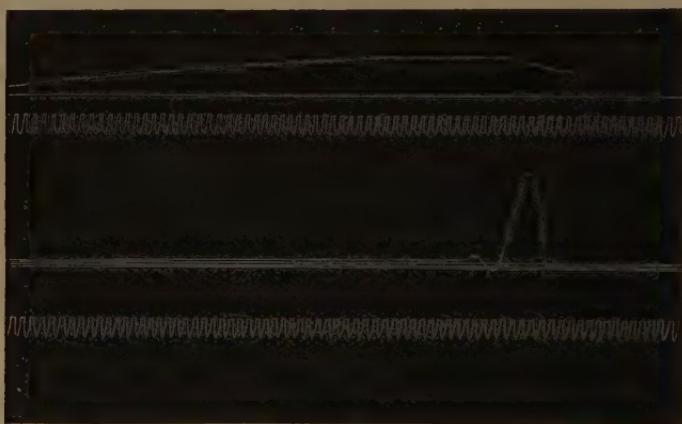


FIG. 16.—Comparison of Contractions of Red and White Muscle of Rabbit stimulated indirectly (M. S. Pembrey).

Upper curve shows prolonged contraction of red soleus and lower curve shows shorter contraction of white gastrocnemius. Read from left to right. Time marking in  $\frac{1}{50}$  secs.

moving surface is called the *graphic method* and it is used to study many physiological processes in detail.

With an isometric contraction the maximum is reached more rapidly as the muscle does not shorten and its viscosity does not delay the shortening.

Different muscles vary in the rapidity with which they contract and relax.

In the same animal there is a relation between structure of muscle and rapidity of contraction, and there are also differences in rate between the muscles of various species of animals.

In the case of muscle we shall now study the effect of different conditions on the curve of contraction and then attempt to draw deductions as to the various processes concerned. The effect of

the strength of stimulus is to cause a difference in the height of contraction, but not in the shape of the curve. This has been studied above.

TABLE I  
RATES OF CONTRACTION OF VARIOUS KINDS OF MUSCLE.

| <i>Muscle.</i>                              | <i>Duration of Simple Twitch.</i> |
|---|-----------------------------------|
| Striated muscle of insect . . . . .         | . 0·003"                          |
| Striated (white) muscle of rabbit . . . . . | . 0·070"                          |
| Striated muscle of frog . . . . .           | . 0·100"                          |
| Striated muscle of terrapin . . . . .       | . 1·000"                          |
| Smooth muscle of mammal . . . . .           | . 10·0"                           |
| Foot of slug . . . . .                      | . 20·0"                           |

**Effect of Temperature on Contraction.** Difference of temperature has a marked effect on the contraction. At low temperatures the various processes proceed more slowly, and at higher

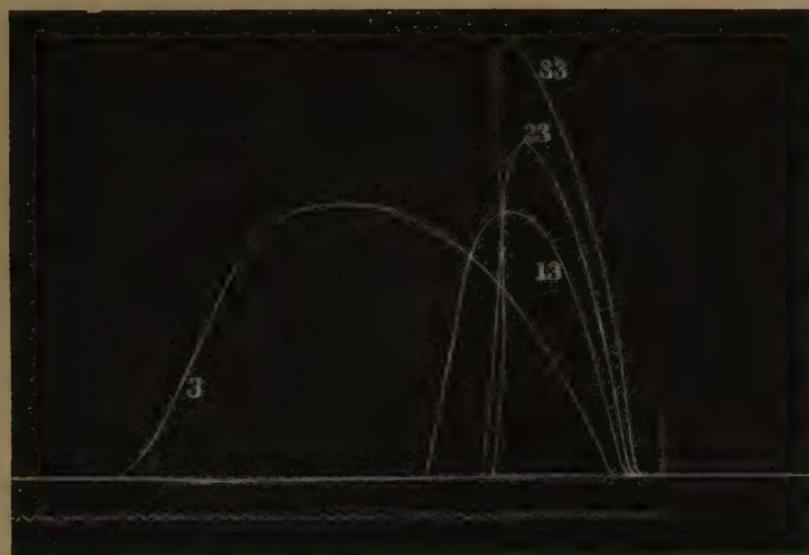


FIG. 17.—The Effect of Temperature upon the Contraction of the Gastrocnemius Muscle (Pembrey and Phillips).

The figures on the curve are the temperatures of the salt solution in which the muscle was immersed. Read from right to left. Time marking in  $\frac{1}{10}$  sec.

temperatures they are quickened. At extreme temperatures the excitability of the muscle is lost. So we must distinguish between the effects of temperature on the resting muscle and on the acting muscle.

Let us examine the curves showing the contraction of muscle in response to stimuli when the muscle is maintained at different temperatures. The curves obtained at several temperatures are shown in Fig. 17.

The first point to note is that at low temperatures all the stages occur more slowly. This is in accordance with most physical and chemical processes, but it has one importance here in that it shows that the fall of the lever depends on processes occurring in the muscle : if the fall of the lever were purely passive due to the stopping of the contraction the lever would fall always at the same rate owing to the action of gravity on the lever and weight. That the fall is delayed shows that the cooled muscle delays the fall of the lever either by increase in viscosity or by some chemical factor which is slowed in rate by a fall of temperature.

Therefore in addition to the latent period and the period of shortening there is a separate process—the period of relaxation. Sometimes the contractions at high temperatures are higher than at low temperatures. This is mainly due to the instrument because a quicker contraction produces greater accel-



FIG. 18.—Effect of Veratrine on Muscle Contraction.

Lower curve normal muscle, upper curve same muscle after treatment with veratrine. The sudden drop at the beginning of the veratrine curve may be due to the presence of some fibres which had not been acted on by the drug. Time marking in  $\frac{1}{2}$  secs.

eration of the moving parts so that these are carried beyond the true curve of shortening by their momentum. In carefully controlled experiments the activity of muscle shows a maximum at  $7^{\circ}$  C. with a lesser contraction above and below this temperature.

The influence of temperature on muscle is not confined to its action on the rate of contraction. Thus on warming muscle slowly it undergoes shortening at certain definite temperatures. Mammalian muscle shortens when heated to  $44^{\circ}$ – $46^{\circ}$  C. or when cooled to  $5^{\circ}$ – $0^{\circ}$  C. and these contractions are reversible if the muscle is cooled or warmed again provided that the temperature change has not gone too far. The muscles of cold-blooded animals show a warm contraction at  $34^{\circ}$ – $40^{\circ}$  C., but no cold contraction. When heated above  $50^{\circ}$  C. a second shortening occurs at about  $60^{\circ}$ – $65^{\circ}$  C. As a similar contraction occurs with inexcitable muscle and tendon the

latter may be due to the fibrous tissue between the muscle fibres (Bottazzi).

Veratrine applied to muscle causes a prolonged contraction. The curve in Fig. 18 shows the result of such an experiment with a slowly moving surface. It frequently happens that the curve shows a sharp fall before the gradual fall of the prolonged relaxation. The prolongation of contraction must be due to some process in the muscle either of a chemical nature or of a physical (such as viscosity of the muscle contents).

**Fatigue.** Another means of showing a prolongation of contraction is by fatigue of the muscle, but this involves a series of changes as follows :

If a muscle is stimulated at short intervals of time it becomes fatigued. If the intervals are too short fusion of contractions, to be described later, is obtained, and if the intervals are too long fatigue is not easily produced.

Two series of curves are given, one on a quickly revolving cylinder with a stimulus at each revolution and the other on a slowly moving surface with rapidly repeated stimuli. In the former case one sometimes records only every fifth contraction as it gives a clearer indication of the series of changes.

The prolongation of the relaxation is shown by the opening out of the curves in each series of contractions, so much so that the muscle does not relax between the stimuli and a certain amount of contraction remains. This is termed *contracture*.

The extent of the shortening is altered. For the first few contractions there may be a slight increase in shortening (*staircase effect*). This is due to an improvement in the condition of the muscle, perhaps a slight warming. Later on the shortening decreases until the muscle ceases to respond to the stimulation. The decrease is not merely due to the rise of the base line because the top of the curve shows a downward tendency. The decrease in the extent of shortening and contracture are best shown on the slowly moving surface where the curve has the appearance of a drawn out  $>$ . If the muscle is allowed to rest it recovers, but the excised muscle, deprived of its circulation, does not completely recover.

**Fusion of Contractions.** If stimuli are repeated at shorter intervals than those used for fatigue, summation can be produced.

The best way to demonstrate this is by means of two stimuli which can be varied in interval. Keeping one stimulus so that it is sent into the muscle at the same point on the drum, and moving the second stimulus so that it acts on the muscle at shorter time intervals (Fig. 21) a series of records is obtained.

When the stimuli are well apart two separate contractions result.



FIG. 19.—Tracing of Fatigue in Frog's Muscle.

The later curves rise more slowly and fall more slowly than the earlier ones. Therefore the lines cross near the top of the curve. (Tracing kindly lent by Dr. W. A. M. Smart.)



FIG. 20.—Exhaustion Curve of Excised and Loaded Gastrocnemius.

Muscle was stimulated with a maximal shock every 5 secs. Exhaustion was complete at the end of 15 minutes. A slight recovery curve is shown at the end of 6 minutes' rest (M. S. Pembrey).

As the stimuli are brought closer together the second contraction commences before the first has completely finished and reaches a higher level than the first. At certain intervals the two contractions are united into one larger result and at a shorter time interval the curve suddenly drops to the height of one of the single contractions.

This series of experiments shows the possibility of fusing more than one contraction to produce a greater result. When the stimuli are too close together, the second stimulus becomes ineffective and only the result of a single stimulus is seen. The latter is due to the *refractory period* because during that period the muscle does not respond to a second stimulus. The refractory period in skeletal muscle corresponds in time to the latent period. With sub-maximal stimuli some effect can be produced by stimuli reaching the muscle within the latent period.

**Genesis of Tetanus.** If more than two repeated stimuli are used the fusion of a series of stimuli can occur as shown in the tracings of Fig. 22 on a slowly moving surface. With infrequent stimuli a series of curves is shown. With more frequent stimuli partial fusion occurs and with still more frequent stimuli, complete fusion into a large smooth curve results. The sudden drop to a smaller contraction is not shown because with repeated stimuli although some stimuli may fall in the latent period the first stimulus beyond the refractory period is effective and the muscle really responds to each second, third, fourth, or other stimulus.

The importance of this experiment is that most contractions in the body are tetanic and single contractions are infrequent in striated muscle.

Many other experiments can be done on muscle. We can calcu-

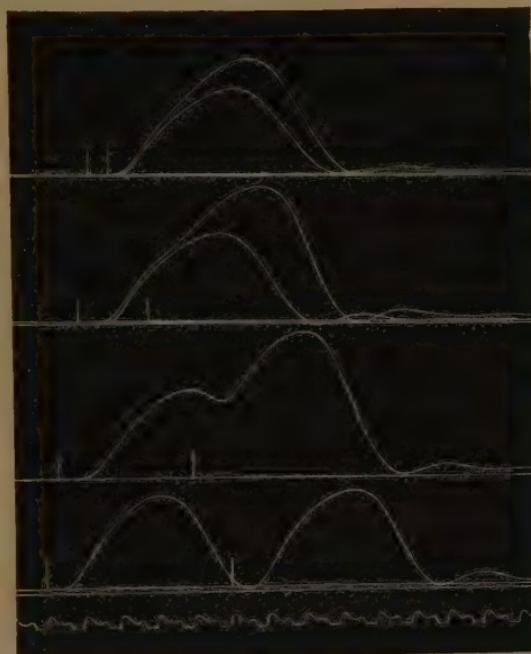


FIG. 21.—Superposition of Two Single Contractions.

The upright lines show the times at which the muscle was stimulated. As the stimuli are sent in closer together, the muscle contractions fuse. Read from left to right (M. S. Pembrey).



FIG. 22.—Genesis of Tetanus.  
The curves show progressive fusion as the frequency of the stimulation is increased.

late the work done by a muscle by varying the weight lifted and multiplying the weight by the height that it is raised. As the weight increases the work done increases to a maximum and falls again as the weight becomes too great to be lifted by the muscle.

The frequency of stimulation at which tetanus occurs depends upon the rate of contraction of the muscle. In excised muscles the temperature at which the experiment is carried out is of paramount importance. Tetanus occurs with insect muscle when the frequency of stimulation is 300 per second, with frog's muscle at the rate of 20–30 per second and with plain muscle at 5–7 stimuli per second.

In human muscle the rate at which it is being stimulated has been estimated by various methods. The tremor of the hand is said to be 10 vibrations per second. Helmholtz used vibrating springs and he found that when the springs were supported on the hand resonance occurred with those that vibrated at the rate of about 20 per second. The pitch of the sound of contracting muscle indicates a vibration of about 40 per second.

Measurements by Piper using the string galvanometer, show the rate at which electrical changes<sup>1</sup> occur in normally contracting muscle.

His results are as follows: For flexors of the arms and fingers the rate of contraction is 47–50 per second, for the deltoid 58–62 per second, for the gastrocnemius, and tibialis anticus, 42–44 per second, for the quadriceps 38–41 per second,

for the masseter 88–100, and for the temporal muscle 82–86

<sup>1</sup> The significance of these electrical changes will be discussed in the next chapter.

per second. Adrian has recorded a much higher frequency in striated muscle.

Many other experiments can be carried out on muscle. We can calculate the work done by a muscle by varying the weight lifted and multiplying the weight by the height that it is raised. As the weight increases the work done increases to a maximum and falls again as the weight becomes too great to be lifted by the muscle.

TABLE II

## WORK DONE BY FROG'S GASTROCNEMIUS WITH VARYING LOADS (BEDDARD)

| Height<br>of<br>Record. | Height to which<br>Weight was<br>Lifted. | Weight<br>in grms. | Work done in<br>gram-<br>millimetres. |
|-------------------------|--|--------------------|---------------------------------------|
| 20                      | 4  | 0                  | 0                                     |
| 20                      | 4  | 50                 | 200                                   |
| 16                      | 3.2                                      | 100                | 320                                   |
| 11                      | 2.2                                      | 150                | 330                                   |
| 9                       | 1.8                                      | 200                | 360                                   |
| 5                       | 1.0                                      | 300                | 300                                   |
| 2.5                     | 0.5                                      | 400                | 200                                   |
| 1.5                     | 0.3                                      | 500                | 150                                   |
| 0.5                     | 0.1                                      | 600                | 60                                    |
| 0.0                     | 0.0                                      | 650                | 0                                     |

The conditions which determine the maximal working power of a muscle depend upon its length and its area of cross section. Length determines the extent of contraction and cross section determines the force that can be exerted. Thus a long thin muscle can lift a light weight farther than a short muscle but it cannot lift so heavy a weight as a short thick muscle.

**Nature of Physical Changes During Contraction.** By causing the muscle to become active in a closed space it can be shown that the volume of muscle remains unchanged. Therefore the decrease in length is compensated by an increase in cross section. This is easily seen by examining one's own muscles during activity when they are observed to swell and are felt to become hard.

In excitation through the nerve the whole muscle contracts at once owing to the wide distribution of nerves in the muscle. If, however, the muscle is excited directly at one end it can be shown that the contraction passes along the muscle fibre in the form of a wave. This is best demonstrated by laying two light levers across a muscle and stimulating it at one end. The lever nearer the point of stimulation is raised by the wave of contraction before the further lever and falls before it. The muscle wave travels at about 3 to 4 metres per second in a frog's muscle at 18° C. As it takes about 0.05 seconds in passing each lever the length of the wave is about 150 millimetres ( $3000 \times 0.05$ ).

Many other experimental methods have been used to investigate

the nature of muscle activity. For instance one can measure the effect of allowing the muscle to commence to contract unloaded, loading it at different time intervals during its contraction. This is accomplished by suspending the weights on the lever and raising the lever by a support placed under it. The muscle now commences to contract without any load on it and the load comes on the muscle after it has shortened sufficiently to "take in the slack" of the thread by which it is connected to the lever.

This method of *after loading* is usually accomplished by a screw placed below the lever. The degree of after loading may be varied by altering the position of the screw. The latent period of the record is longer with after loaded muscle. Just as the shortening of the isotonic contraction shows a quicker rise than the increase in tension of an isometric contraction, so also is this longer delay due to the time required for liquid to be moved in the muscle. There is a relation between the tension exerted by a muscle, and

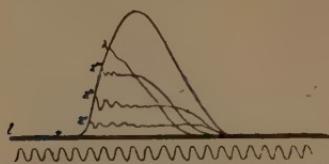


FIG. 23.—Curves of Arrested Contractions of Unloaded Muscle (Kaiser).

The records show that the lever is kept pressed against the arresting stop, therefore that the contraction lasts for a certain length of time and passes off slowly.

contraction lasts for a definite time interval and relaxation occurs gradually. When the contraction is arrested before much shortening has occurred the duration of the contraction keeps the lever lifted against the stop for some time, but when the arrest occurs with almost maximal shortening of the muscle the duration of this degree of shortening is seen to be less. This indicates that the duration of a muscle twitch depends upon the degree of shortening of the muscle at which the measurement is made.

The contraction of muscle enables it to exert a certain tension or to shorten to a certain extent. The tension exerted is dependent on the concomitant degree of shortening. The rate of shortening depends upon the tension on the muscle and the degree of shortening already produced. Thus the rate of shortening is zero when the tension is such that no shortening can occur and when there is no tension the muscle having already shortened to its maximum. The maximal rate of shortening occurs with a fully extended muscle

the degree of shortening at which the measurement is made. So also is there a relation between the amount of shortening, and the rate at which further shortening can occur. Therefore the latent period becomes more prolonged the greater the degree of after loading.

By placing a screw above the lever the contraction can be stopped after a certain degree of shortening has occurred. These *arrested contractions* show that the wave of

with minimal weight pulling on it. The increased latent period with after loaded muscle is due to the fact that there is a measurable rate of shortening with all conditions of the muscle.

Arrested contractions show that the duration of the twitch also depends upon the extent of shortening at which the duration is recorded.

The force exerted by a muscle depends upon its area of cross section. The effective component of the force depends upon the angle at which the pull is applied to the bone. The various fibres of the muscle may pull in slightly different directions. Thus in a triangular muscle such as the deltoid the anterior fibres may pull the arm forwards, whilst the posterior fibres may pull it backwards. The whole muscle lifts the arm from the side. In any muscle the shape of the muscle and its direction of pull requires a careful mathematical calculation, in order to determine its effective pull on the bone on which it is inserted.

The various mechanical phenomena discussed in this chapter are accompanied by other changes. Some of these will be studied in the next chapter and others will be deferred to Part II.

## CHAPTER III

### HEAT AND ELECTRICAL CHANGES IN MUSCLE

When a muscle contracts there are other changes in addition to an increased tension. The chemical changes are dealt with in a later part of this book, but here we can consider two physical phenomena, namely production of heat and of electricity. These are not so easily demonstrated as the mechanical changes described in the preceding chapter.

#### HEAT PRODUCTION

Heat production can be shown crudely by the heating effect of muscular exercise on the whole body or by a sensitive thermometer placed amongst a mass of contracting frog's muscles, but for finer changes a much more elaborate arrangement is required.

The modern development of heat measurement in muscle is by means of a thermopile. In its simplest form this consists of junctions

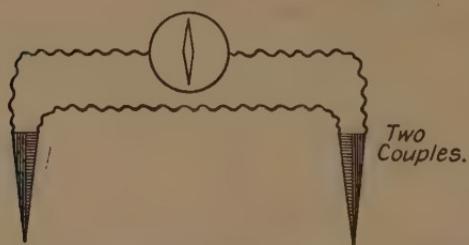


FIG. 24.—Diagram of a Pair of Thermocouples connected to a Galvanometer (Waller).

of two dissimilar metals. When one junction is warmed or cooled an electrical potential is produced. A sensitive low-resistance galvanometer is required in order to show the direction and amount of current produced. Increased delicacy is obtained by using a series of junctions;

Heidenhain (1877) used fifteen junctions in contact with the muscle. These junctions must be as fine as possible, so that they are rapidly heated and do not absorb too much of the heat in being warmed up. Such a series of junctions must be arranged so that the alternate junctions are in contact with the muscle, otherwise the potentials in opposite directions would neutralize each other.

In the case of the simple thermopile it is the difference in temperature between the two junctions which produces the current. In the compound thermopile the muscle lies midway between the framework so that the junctions are alternately in contact with the

muscle and on the outer side of the frame. Therefore the small electrical potentials are all in the same direction and add up to produce a greater effect in the galvanometer. In such an apparatus it is essential that the external junctions should be protected from accidental variations in temperature so that the effect may be produced solely by the change in temperature of the muscle. The apparatus is standardized by adding a known amount of heat to the muscle (usually by an alternating current passed through the dead muscle at the end of the experiment). This calibration gives the heat production directly. One must remember that the specific heat of muscle is about 0·83, so that the heat produced will cause a greater rise of temperature than if the same weight of water were substituted for the muscle. Measurements of heat production in muscle show that every alteration in muscle produces a heat change. Gain or loss of energy in any system is usually accompanied by a heat change, so that muscle is not exceptional in this respect. The mere extension of a muscle by a weight causes a fall in temperature, which is reversed when the weight is removed. These relationships have not been finally determined, so they need not be described in detail.

Muscle contraction produces heat and it has been shown that approximately half the heat production occurs in the early stage of contraction. These measurements having been made during short periods of tetanus, cannot unfortunately be compared with the changes in a single twitch. The heat produced as the result of contraction of muscle is not all set free during the period of contraction. If a reversible system is changed from one state to another with a gain or loss of energy there must be an equal loss or gain if the system is to be restored to its former state. Macdonald has expressed this relationship as follows: "A muscular contraction, in short, is akin to the release of a spring previously wound up by heat set free during a long-continued process of combustion."

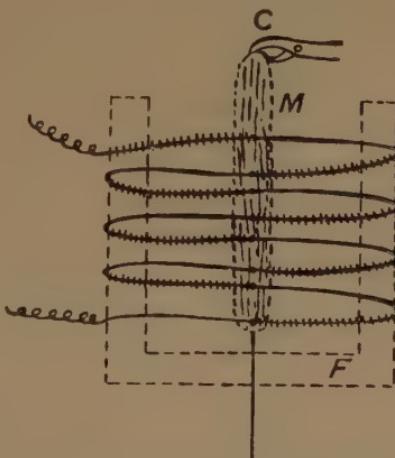


FIG. 25.—Diagram of Thermopile  
(Redrawn from A. V. Hill in the *Journal of Physiology*).

The muscle *M* held by the clamp *C* lies over the series of junctions. The wires are wound on a frame *F* so that the alternate junctions lie under the muscle and on the outer surface of the frame. To show the junctions clearly one kind of metal is indicated by dashes crossing the line of the wire. If when the junction is warmed the current flows from the plain wire to that with dashes across it, as the muscle becomes warmer the current will be in the same direction at each junction in contact with the muscle.

measurements having been made during short periods of tetanus, cannot unfortunately be compared with the changes in a single twitch. The heat produced as the result of contraction of muscle is not all set free during the period of contraction. If a reversible system is changed from one state to another with a gain or loss of energy there must be an equal loss or gain if the system is to be restored to its former state. Macdonald has expressed this relationship as follows: "A muscular contraction, in short, is akin to the release of a spring previously wound up by heat set free during a long-continued process of combustion."

If a muscle is prevented from doing external work all the energy of its contraction will be converted into heat. Measurements of heat production by A. V. Hill have shown that the amount of heat set free when a muscle is prevented from contracting is approximately equal to the heat production during the process of recovery after contraction. This result is a direct confirmation of the view of

Macdonald given above. A. V. Hill has further shown that if a muscle contracts in an atmosphere of nitrogen no delayed heat production occurs. Fig. 26 shows the effect on the galvanometer of the cooling of a muscle following contraction. The control curve shows the rate of cooling of the same muscle after it had been killed and warmed by an alternating electric current.

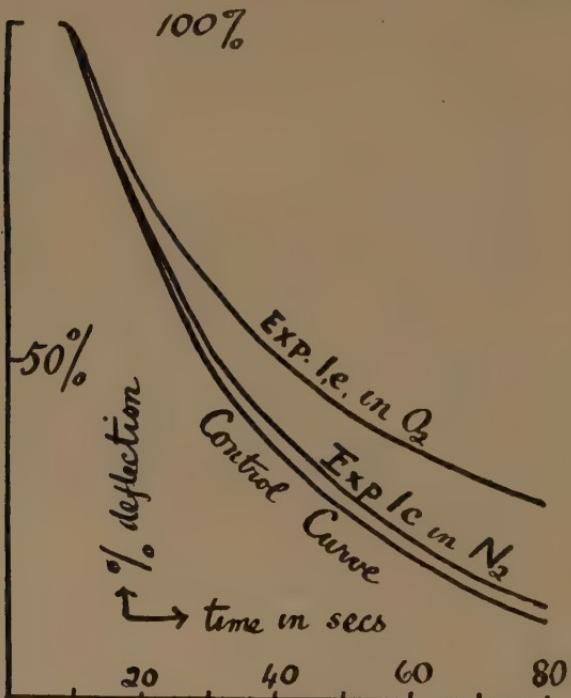


FIG. 26.—Galvanometer Deflection showing Fall of Temperature of Muscle after Excitation in Nitrogen and in Oxygen, and after being Warmed when Dead as a Control (A. V. Hill in the *Journal of Physiology*).

The rate of cooling of the living muscle in nitrogen practically corresponds with that of the dead muscle. The living muscle in oxygen cools more slowly, showing continued heat production during and after relaxation.

Ordinates = per cent. of maximum deflection of the galvanometer.  
Abscissæ = time in secs.

in the presence of oxygen the muscle does not cool so rapidly. The interpretation of this result is that the muscle cools less rapidly because it is kept warmer by oxidation as the result of the contraction. The evidence therefore points to muscle contraction being accompanied by an explosive non-oxidative change followed by a process of oxidation. As the energy of the restorative process must at least equal the initial change the effi-

ciency of a simple twitch must be less than 50 per cent. In other words the amount of energy which can be set free as kinetic energy is about half of the total energy set free as heat when the heat output is measured by a thermopile in the presence of oxygen.

Superimposed on these two main energy exchanges are subsidiary variations due to mechanical effects on the muscle. These smaller changes are similar to the temperature variations produced by stretching and relaxation of any fibrillar structure.

### ELECTRICAL CHANGES

The electrical changes of muscle require a knowledge of physical chemistry for their interpretation as all chemical changes are accompanied by alterations in electrical potential. Therefore the present discussion will be limited to a description of methods and results. To measure the electrical changes in muscle requires electrodes for leading off the potential and an instrument for measuring the potential. The current is related to the potential by Ohm's Law

$$C = \frac{E}{R} \text{ where } C = \text{current in ampères, } E = \text{potential in volts and}$$

$R$  = resistance in ohms. It is potential that is produced in a chemical system, hence one measures the muscle current in volts.

**Non-polarizable Electrodes.** The contact of a metallic electrode with a moist conductor always produces an electrical potential (see p. 148). As this contact potential is generally large and variable it is necessary to use some form of electrodes which avoids these changes in potential. If two electrodes are used and if their potential differences are of the same fixed value, by arranging the electrodes so that the potentials are in opposite directions no difference of potential will be shown by the recording instrument. Such forms of electrodes are called non-polarizable electrodes.

TABLE III  
FORMS OF NON-POLARIZABLE ELECTRODES

| Metal.                             | Solution.   | Contact with Muscle.                             |
|------------------------------------|---|--|
| Zinc . . . . .                     | Saturated solution of zinc sulphate               | Through a solution of chloride (Ringer solution) |
| Mercury (calomel electrode)        | Ringer solution saturated with mercurous chloride | Direct   |
| Silver coated with silver chloride | Ringer solution                                   | Direct   |

These pairs of electrodes have equal and opposed potentials so that any change shown by the galvanometer is the result of potential differences between the muscle and the Ringer solution in contact with it. In order to measure the electrical potential in living

tissues three types of instrument are used, namely the capillary electrometer, reflecting galvanometer and the string galvanometer.

**Electrometers and Galvanometers.** An electrometer measures the electrical potential of a system. The form that is used for investigations in physiology is the *capillary electrometer*. This consists of a narrow glass tube containing mercury dipping into a vessel containing 10 per cent. sulphuric acid. As the capillary is very narrow mercury will travel down it only when pressure is applied to the tube containing mercury. The extent to which the mercury will be forced down the tube depends upon the surface tension between the mercury and the sulphuric acid. An alteration of surface tension can be brought about by changes in electrical

potential at the mercury-acid surface. The mercury always passes along the capillary tube in the direction of the current. In order to make the response very rapid the capillary is made very narrow. In this way the extent of movement is reduced, hence there is very little inertia. The extent of movement is so slight that it cannot be seen unless the capillary is magnified. A microscope objective is therefore used and by means of a strong light

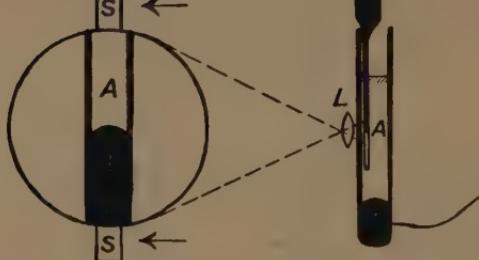


FIG. 27.—Diagram of Capillary Electrometer.

The mercury is forced into the capillary by pressure as indicated by the arrow in the tube. An image of the capillary is formed by the lens *L*. The image is superimposed on the slit *SS*, which has been represented as turned through 90° so that it can be seen on the plane of the paper. Movement of mercury down the capillary will cause an upward movement of the image of the mercury to fill the space *A* which corresponds to the portion of the capillary containing acid. The shadow of the mercury is photographed on the sensitive surface which moves behind the slit in the direction indicated by the two arrows.

the magnified image of the mercury column can be photographed. The mercury causes a shadow on the brightly illuminated field. If this shadow falls on a slit behind which is a moving photographic plate the changes of potential will be shown by the movement of the shadow.

The record of the beating heart of a toad (Fig. 28) is more complicated than that of skeletal muscle. The record shown in Fig. 28 gives a tracing of the contraction of the ventricle by the method shown in the lower part of Fig. 10, recorded simultaneously with the record of the capillary electrometer. The non-polarizable electrodes were calomel electrodes connected to the surface of the ventricle by wicks moistened with Ringer solution.

*Reflecting Galvanometers.* These are either a magnetic system surrounded by coils of wire or a coil of wire in a magnetic field. The current to be measured passes through the coils and causes a turning of the suspended system. These galvanometers can be made very sensitive but their period is long. They are used for long continued currents such as those from tetanized muscle. The movement of the suspended system is magnified by a mirror which by turning causes deflection of the image of a source of light.

The reflecting galvanometers used in physiological investigations generally have a very high resistance, therefore the movement of the image of the spot of light is almost proportional to the change of potential; low-resistance galvanometers are used for recording the current produced by thermo-couples.

*String Galvanometer.* This is really an elaboration of the above. The moving part is reduced to the smallest possible dimensions and consists of a single fibre of glass or quartz coated with silver. The two ends of the fibre are fixed and the tension on the fibre can be varied by a delicate adjustment.

When a current is passed through this fibre it is deflected across the poles of a magnet. In order to make this form of instrument sufficiently delicate the magnetic field is made very strong by the use of a powerful electro-magnet. The poles are brought close together and they are bevelled so as to make the field very concentrated. The movement of the fibre is rapid but minute. In order to make the movement visible it is magnified by an optical system. As the movement is at right angles across the poles of the magnet it is necessary to bore a hole through both poles and view the fibre through these holes.

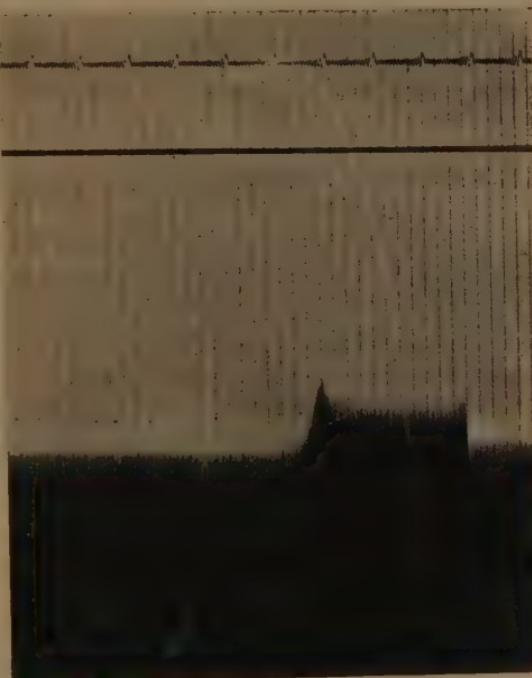


FIG. 28.—Record of Contraction of Toad's Ventricle.

Electrical record by capillary electrometer (see Fig. 27). Mechanical response superimposed by optical method shown in Fig. 10. Read from right to left. Time marking in  $\frac{1}{2}$  secs. (Roaf).

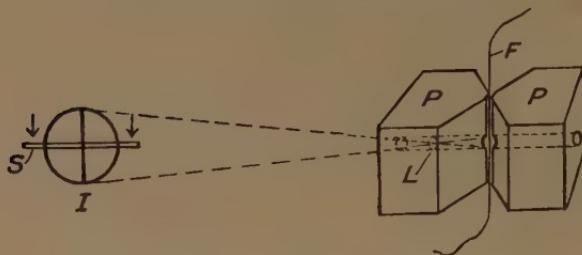


FIG. 29.—Diagram of String Galvanometer.

A current through the filament  $F$  causes it to move across the poles ( $P, P$ ) of the magnet perpendicular to the plane of the paper. A lens  $L$  forms an image  $I$  of the thread across the slit  $S$  of the camera, which has been represented as turned through  $90^\circ$  so that it can be seen on the plane of the paper. The photographic surface moves behind the slit as indicated by the two arrows.

#### RESULTS OBTAINED BY MEASURING ELECTRICAL CHANGES IN MUSCLE

**Current of Injury.** Using non-polarizable electrodes and one of these means of measuring, it is found that the surface of an *uninjured* muscle with parallel fibres shows no electrical potential, but if the muscle is injured, as by burning with a hot wire, a current is present.

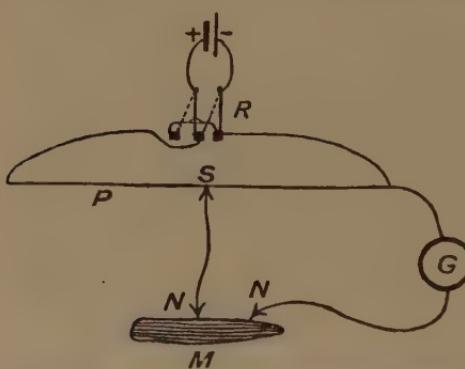


FIG. 30.—Diagram of Compensation Method for Measuring Electrical Potential.

A source of potential above is connected to the potentiometer  $P$  by a reversing key  $R$ . The muscle  $M$  is connected to the galvanometer  $G$  and slider  $S$  of potentiometer by two non-polarizable electrodes  $N, N$ . When the slider is in such a position that no current flows through the galvanometer, the potential at the muscle is to the potential of the battery as the length of the uniform resistance wire to the right of the slider is to the whole length of that wire.

The direction of the current is from the uninjured portion through the external circuit to the injured area. Comparing the muscle to a voltaic cell the injured area is negative to the uninjured. Sometimes there is confusion introduced by considering that the current must be completed in the muscle so that in the muscle the injured part is positive. This is the same

ent. Taking a cross section through a muscle as a typical injury the greatest current is produced when the two electrodes are on the centre of the cross section and on the surface of the muscle as far as possible from the injury respectively. If the muscle is injured in two places the greatest potential is from the centre of one injured area to the mid-point between the two injuries. This is known as the current of injury.

The direction of the

condition as a voltaic cell in which the negative pole is positive inside the cell. It is clearer to regard the muscle as a voltaic cell and to consider the negative area as that to which the external current flows.

The electrical potential can be determined by calibrating the measuring instrument or by opposing the muscle potential by that from a potentiometer so that the measuring instrument indicates no current flowing through it. The latter is called a compensating potential, and if no current flows the pressure (or potential) of the two currents is the same. As the voltage from the potentiometer is known the voltage of the muscle-current is known when the two are balanced.

**Current of Action.** If an injured muscle is stimulated after the injury current has been compensated, a current is recorded, but in this case it is in the opposite direction to the injury current : therefore this is frequently spoken of as the negative variation or current of action. More intimate analysis of the electrical conditions in muscle consists in studying the conditions during the passage of a muscle wave. Usually when the muscle is active the whole muscle is contracting at the same time, so that there is no difference between one part of the muscle and another. It is only by injuring the muscle that one can show the difference due to muscle activity. The cause of the current of action is that there is less potential between active and injured muscle than between resting and injured muscle. The current in the reverse direction is due to the excess of the compensating potential over the potential due to the injury. Consequently active muscle is negative to resting muscle. We can demonstrate this by repeating the experiment on the muscle wave (p. 33) only using non-polarizable electrodes instead of (or in addition to) the light levers.

*Diphasic Variations.* With such an arrangement the muscle wave reaches the electrodes and passes under them but reaches the second electrode after the first. Depending on the distance apart of the electrodes the actual conditions may vary in their time relations, but we can think of three stages : (1) When the muscle wave has reached one electrode but not the other. (2) When the muscle under both electrodes is active,<sup>1</sup> and (3) when the muscle wave has passed the first electrode but is still under the second. Corresponding to these stages the recording instrument shows that the first electrode becomes negative to the second : then both electrodes become equipotential : finally the second electrode is

<sup>1</sup> If the electrodes are far enough apart one might have the condition in which the muscle wave is between the electrodes and the muscle at rest under both electrodes.

negative to the first. This double swing of the current is called a diphasic variation because the record shows a swing first in one direction then in the other. The single swing during the activity of an injured muscle is distinguished as a monophasic variation.

We see therefore that injured muscle is negative to resting un-

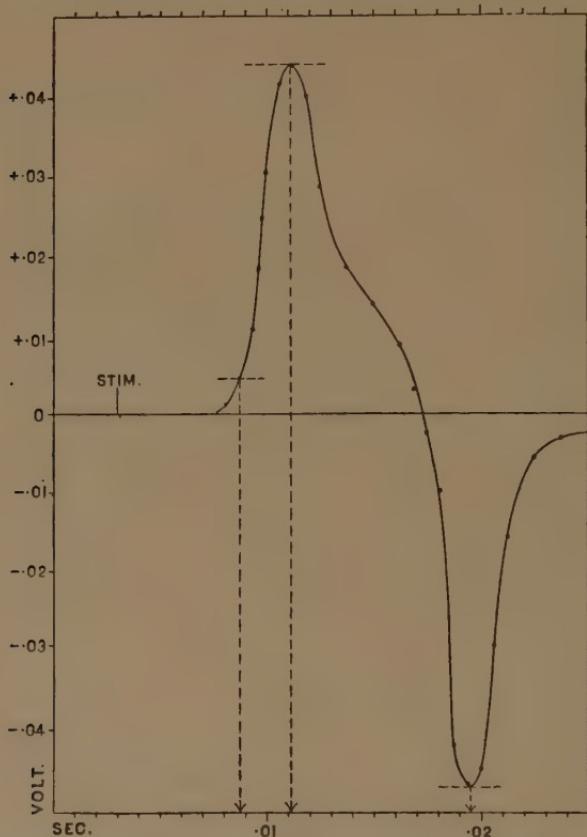


FIG. 31.—Actual Potential Differences obtained by Analysis of a Record by the Capillary Electrometer of the Diphasic Response of a Sartorius Muscle at 18° C. (Keith Lucas).

Ordinates = potentials in volts. Abscissæ = time in secs.

injured muscle and that active muscle is also negative to resting uninjured muscle. The difference between injured and active muscle is less than that between injured and resting muscle, so that the compensating potential causes a record of a current in the opposite direction to the injury current. If the injury current is not compensated activity of muscle shows merely a decrease in the injury potential. The effect of activity is not so great as injury so

that some current is still observable in an injured muscle during contraction.

The electrical response occurs in the early part of the stage of contraction. When the whole muscle is contracted the surface is isoelectric (p. 42), and therefore both resting and contracted muscles are isoelectric. Other tissues show electrical potentials. Changes in potential in nerves will be described later.



FIG. 32.—Diagram showing Electrical Potential Differences from Whole Eye and from Retina (Waller, *Human Physiology*, Longmans, Green & Co.).

*Retinal Currents.* A "current of rest" runs through the eyeball. The current may be due to injury to the optic nerve. When light falls on the retina the potential alters. Usually there is an increase in potential when light falls on the retina

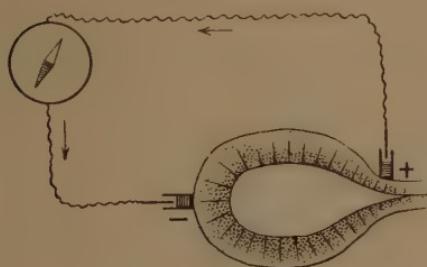


FIG. 33.—Diagram showing Electrical Potential Differences from a Gland (Waller, *Human Physiology*, Longmans, Green & Co.).

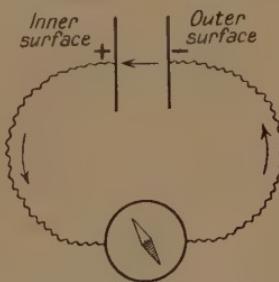


FIG. 34.—Diagram showing Electrical Potential Differences from the Skin (Waller, *Human Physiology*, Longmans, Green & Co.).

and when the light is cut off. The external or choroidal surface is negative.

*Gland Currents.* The surface is negative to the hilum when at rest and when the gland becomes active the potential is in the same direction but increased in value.

*Skin Currents.* There is a difference in potential between the outer and inner surfaces of the skin. The outer surface is nega-

tive. When sweat is being secreted the potential difference is increased.

*Blaze Currents* are produced in any living tissue after it has been strongly tetanized. They are a sign of life.

*Electrical Organs.* A number of fishes are known which can give electric shocks when they are handled. The situation of the electrical organs varies in different species but in most cases the electric organ is a modified form of muscle. It is innervated by one large nerve cell with branching fibres so that the whole structure discharges at once. The following have electrical organs : Torpedo, Gymnotus, Mormyrus, Malapterurus and the skate.

The potential differences in the various tissues are sufficient to stimulate nerves. The following three experiments are of interest :

*Rheoscopic Muscle Nerve Preparation or Secondary Twitch.* Two muscle nerve preparations are made which we shall designate A and B. The nerve of B is laid on the muscle of A. The nerve of A is stimulated and with every contraction of muscle A muscle B also responds. This result is due to the stimulation of the nerve of B by the currents of action of muscle A.

*Stimulation of a Nerve by its own Current of Injury.* A muscle nerve preparation is made and the nerve is laid across two rolls of china clay moistened with Ringer solution. The cut end of the nerve touches one roll and an uninjured part of the nerve touches the other roll. The two rolls lie near the edge of a glass plate with one end of each roll turned over the edge of the plate. Every time a vessel of saline is brought up so as to touch the ends of the two rolls the muscle contracts. The current due to the potential difference between injured and uninjured nerve is sufficient to stimulate the nerve when the circuit is completed through the vessel of saline. This is similar to Galvani's experiment in which a cut end of a nerve is allowed to touch the muscle to which it belongs. Every time the cut end of the nerve touches the muscle the muscle contracts. This experiment is of great historical interest. Galvani in 1786 noticed that the muscles of a frog's leg suspended on an iron railing by a copper hook contracted whenever the leg touched the iron railings. Volta claimed that the excitation was due to the two dissimilar metals in contact at one point and connected by the tissue fluids at two other points. Galvani's experiment showed that metals are not necessary for the stimulation.

The controversy is interesting because of its association with the galvanic cell and the voltaic pile.

Thus we see that accompanying mechanical changes in muscle there are thermal and electrical changes. Similar changes are

found in other tissues and they are probably present in all forms of activity.

NOTE.—For further reference on these subjects see J. Burdon Saunderson, "The Mechanical, Thermal and Electrical Properties of Striped Muscles," and F. Gotch, "The Physiology of Electrical Organs," both in *Textbook of Physiology*, edited by E. A. Schafer (Oxford Medical Publications), pp. 352 and 561; W. Biedermann, *Electro-physiology*, translated by F. A. Welby, 1896 (Macmillan & Co.); A. V. Hill, various papers on Heat Production in the *Journal of Physiology*.

## CHAPTER IV

### RESPIRATORY MECHANICS

In the preceding chapters the bodily movements associated with progression and other complicated acts have been studied. In addition to such movements the rhythmical movements of respiration can be observed. These movements continue even when the individual is lying down and asleep. The result of the respiratory movements is that the lungs act as a pair of bellows. Air is drawn into the lungs and expelled again during each cycle of respiration. We can study this process of respiration in several different ways. The simplest observation to make is to count the number of respirations. In an adult man during resting conditions the respirations are from sixteen to eighteen per minute.

**Measurement of Expansion of the Chest.** A tape measure pulled firmly round the chest measures the circumference of the chest. If the measurement is made at the beginning and end of inspiration the difference will show that the circumference of the chest is increased during the period in which air is being drawn into the lungs (inspiration). The diameters of the chest can be measured by a large pair of calipers called a *cyrtometer*. By means of this we can determine whether the increase in circumference is due to an increase in one direction or in several, and we find that the diameters of the chest increase antero-posteriorly and laterally. In order to record these movements we can use a framework like the cyrtometer to one limb of which a movable rod is attached. One end of this rod is kept pressed against the chest wall by a spring. As the chest expands the rod will be pushed out against the spring. By a system of threads, pulleys and levers, the movement of the rod to and fro in the cyrtometer frame can be recorded. The usual method for recording movements of respiration is, however, some form of air transmission.

*Marey's Tambours.* The principle of recording by air transmission is best explained by a reference to Marey's tambours. Each tambour consists of a rigid case open at one side and with a tube leading into the casing. The open mouth of the case is closed by a flexible membrane which is usually made of thin indiarubber. In the membrane is a rigid disc with a button at its centre. Two tam-

hours are connected together by rubber tubing. One tambour (A) is the receiving tambour and the other (B) is the recording tambour. Above the recording tambour is a lever which rests upon the button fixed to the disc on the membrane. There is a T-shaped junction on the connecting tubing so that the air pressure in the tambours may be suitably adjusted. The action of these tambours is that when the button of A is pressed inwards there is a rise of pressure which is transmitted along the connecting tube to B with the result that the lever is raised. On the other hand, if the object against which A is pressed recedes, the weight of the lever on B forces air through the tube because the pressure can force the membrane of A outwards. The air pressure in the system must be so regulated that the lever is supported by the membrane of B when the button of A is against the object the movements of which are being measured. When the membrane of A is unsupported the weight of the lever should be able to force it outwards.

**Methods for Recording Movements of the Chest.** The application of the above principle enables us to record the movements of the chest. All that is needed is some means of causing variations of pressure inside the recording tambour.

A rubber balloon if placed between an inextensible band, such as the waistcoat, and the chest, will be compressed with each expansion of the chest. This balloon can be slightly distended with air and connected to a recording tambour. Another form of receiving apparatus is to use a drum mounted on a curved chest piece. Both ends of this drum are covered by an elastic

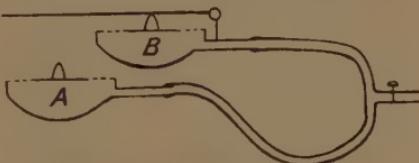


FIG. 35.—Marey's Tambours.

Pressure on button of A will force air along the connecting tube distending the membrane of B so that the lever is raised. The side tube is used to adjust the pressure so that the maximum sensitivity is obtained.

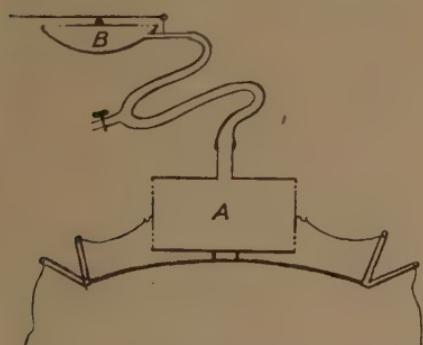


FIG. 36.—Diagram of Stethograph.

A = drum with extensible ends. The curved base rests against the chest and the strings attached to the levers are tied round the thorax. When the chest expands the ends of A are drawn out, and the lever falls because the air is sucked out of B by the distension of the ends of A.

membrane. To the two membranes are attached tapes which can be tied round the chest. When the chest expands the tapes pull on the membranes causing them to be drawn outwards. Pulling

the membranes outwards causes a fall in pressure with a sinking of the lever of the recording tambour. The ends of the drum may be set at an angle so that the tapes round the chest pull at right angles to the membrane or the direction of pull may be altered by levers, as shown in Fig. 36, so as to pull at right angles to the straight drum. Many modifications of these recorders are used. The movements of the chest wall can also be observed by means of X-rays. The changes in size of the thorax are accompanied by the movement of air into and out of the lungs. The volume of air breathed can be measured and compared with the changes in size of the thorax.

**Measurement of the Volume of Air Breathed.** The simplest method of measuring the volume of air breathed is to close the nostrils and to breathe through the mouth by means of a wide tube into a spirometer. The spirometer (Fig. 37) is a metal chamber inverted

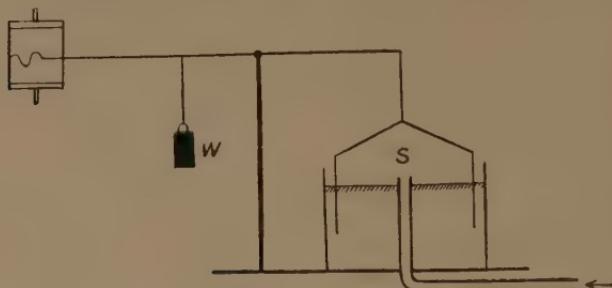


FIG. 37.—Diagram of Spirometer.

The bell is counterpoised by the weight  $W$ . When air passes in the direction of the arrow into the space  $S$  above the liquid, the spirometer rises and the lever marks a downstroke.

into a vessel containing water. The metal chamber is balanced by a weight, or instead of a lever and weight it may be balanced by weights running over pulleys. The movements of the gasometer can be recorded by a writing point. If the spirometer is standardized by using known volumes of gas the volume-changes can be measured. Another form of spirometer consists of a concertina-like structure. Two rigid ends are united by soft flexible material so that the change in volume takes place by the movement of the two rigid ends from and to each other.

Another method whereby the volume of air breathed can be measured is to use two valves. The simplest form of valves are known as Müller's valves. They consist of two bottles containing a little liquid. Into each bottle are inserted two tubes, one of which dips below the level of the liquid. As represented in Fig. 38 the to-and-fro movements of respiration are converted into a unidirectional flow of gas.

Other forms of valves consist of rubber or metal flaps which open and close with each respiration. These also convert the respiratory movement of gas into a unidirectional flow. The volume of the unidirectional flow can be measured by a spirometer or by some sort of gas meter.

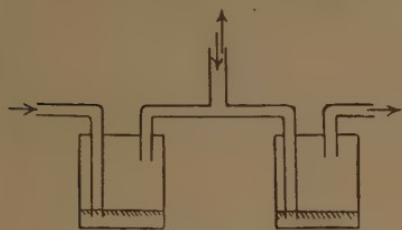


FIG. 38.—Müller's Valves.

This diagram shows how to-and-fro movement of air in the T-piece will cause movement of air in the direction of the arrows. Inspiration will cause air to bubble through the left-hand flask whilst the long tube in the right-hand flask is closed by the water in the flask. Expiration will force air through the right-hand flask whilst the long tube in the left-hand one is blocked by the liquid in the flask.

The following experiment shows that the volume-changes of the chest correspond to the volumes of air breathed. If the whole body is enclosed in an air-tight box no change in volume occurs during respiration. If, on the other hand, the head is left outside the box and an air-tight collar is placed round the neck a

change in pressure occurs in the box during respiration.

This box is connected to a recording apparatus and the whole is standardized so that the record can be translated into volumes. It is found that the volume changes of the body agree with the volumes of gas breathed as measured by a spirometer. Therefore the change in volume of the chest represents the volume of air which enters or leaves the chest.

**Volumes of Air breathed during Respiration.** The volume of air breathed varies under different conditions. We can average the movements of the spirometer or we can measure by the use of valves the total volume of air passed through a meter. The total volume divided by the number of respirations gives the average amount breathed per respiration. During quiet respiration there is a to-and-fro flow of air. This in-and-out movement resembles the ebb and flow of the tide, hence the air breathed during a quiet respiration is called *tidal air*. Its average value for an adult man is about 500 cubic centimetres. At the end of a quiet inspiration it is possible by a deep inspiration to draw in a large quantity of air. This extra volume is called the *complemental air*; it is about 2,000 cubic centimetres. Likewise at the end of a quiet expiration it is

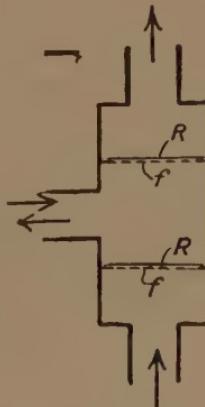


FIG. 39.—Respiration Valves.

Rubber discs (*R*) lie on perforated grids (*f*). To-and-fro movement of air at the side entrance as represented by the double arrows causes air to enter by the lower opening and escape from the upper opening. The lower rubber flap lifts when air is inspired and the upper one when air is expired.

possible by a deep expiration to force out a further volume of about 1,500 cubic centimetres : this is called the *supplemental air*. The total volume that can be drawn in or forced out by any one respiratory movement is the sum of these three ( $500 + 1,500 + 2,000$ ) = 4,000 cubic centimetres. This volume is called the *vital capacity*.

Even at the end of a deep expiration there is still some air left in the lungs. The volume of this *residual air* is measured as follows. At the end of a deep expiration, with the nose closed, the subject breathes from a bag containing a known volume of pure hydrogen. Several deep inspirations and expirations are made so that the

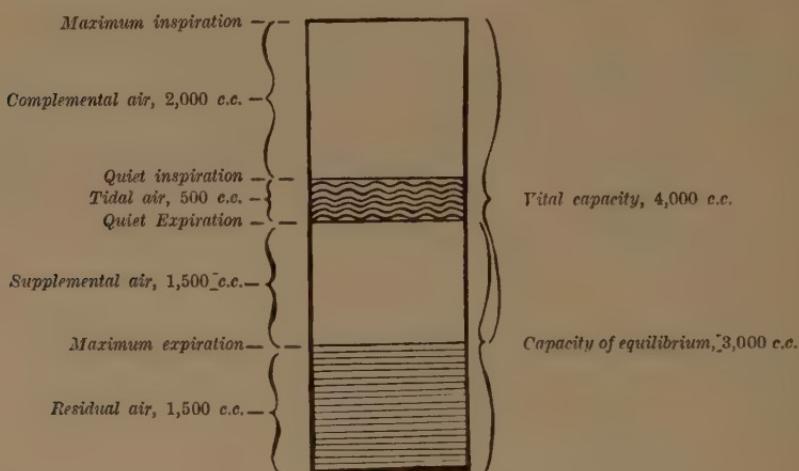


FIG. 40.—VOLUMES OF AIR IN LUNGS. (After Waller.)

The to-and-fro movement of 500 c.c. of tidal air is represented by waves. The residual air which remains in the lungs after the deepest expiration is represented by horizontal lines. The brackets on the right show (a) the vital capacity or the volume of air which can be breathed out between a maximum inspiration and a maximum expiration, (b) the capacity of equilibrium, i.e. the amount of gas with which the tidal air is diluted.

indifferent gas, hydrogen, is evenly distributed throughout the lungs and the bag. The subject ends by a deep expiration so that the bag contains the same volume as at the beginning. Then the gas in the bag is analysed to see what percentage of hydrogen is left. For example after breathing into and out of a bag containing 4,000 cubic centimetres of pure hydrogen, 4,000 cubic centimetres of 75 per cent. hydrogen are left. Therefore there are 3,000 cubic centimetres of hydrogen left, and 1,000 cubic centimetres have passed into the lungs. As the composition of the gas in the lungs should be the same as that in the bag, the 1,000 cubic centimetres represent 75 per cent. of the volume left in the lungs, therefore the volume of the residual air is

$$\frac{3}{4}x = 1,000 \quad \text{or} \quad x = \frac{4}{3} \times 1,000 = 1,333 \text{ cubic centimetres.}$$

The mechanism by which these volume changes are caused is the movement of the thorax. The thorax consists of a long framework formed by the ribs, sternum and vertebræ. The spaces between the bones are filled by muscles and membranes so that the thorax forms a closed truncated cone.

**Mechanism of the Movements of Ribs and Sternum.** The ribs are articulated to the vertebræ and slope downwards and forwards. The upper ribs are attached to the sternum through cartilages. When the ribs are raised the anterior ends sweep upwards in the arc of a circle. If the ribs were horizontal the distance from the vertebræ to the sternum would be a maximum ; when the ribs are depressed the sternum approaches the vertebral column. The ribs form the radii of circles of which the centre is the articulation of the rib to the vertebral column. At the same time that the ribs are raised they are rotated. The convexity of the ribs which is directed downwards in the expiratory position turns outwards as the ribs are raised. This movement increases the width of the chest because each rib acts as the radius of a circle directed towards the side. Thus the lateral diameter of the chest is also increased. (Compare the movement of the handle of a pail as it is moved from the vertical towards the horizontal.)

The movements of the ribs are brought about by the action of muscles. The resting position of the chest is that taken at the end of a quiet expiration. This position is maintained by the action of gravity and by the elasticity of the thoracic structures. The ribs being attached by their heads to the bodies of the vertebræ the weight of the chest wall and structures attached thereto pull the anterior ends of the ribs downwards. The cartilages of the ribs support the thorax in this position and the inward pull of the lungs (see p. 55) will tend to make the chest wall collapse. Thus the position is a balance of weight and elastic forces. From the position of rest muscles can cause the ribs to rise, as in inspiration, or to sink as in forced expiration. The ribs are raised first of all by external inter-costal muscles. These muscles run from one rib downwards and forwards to the next rib below, and by their contraction they draw their origin and insertion closer together, and the only way in which this can be accomplished is by raising the ribs.

The mechanics of the external intercostal muscles is shown in Fig. 41. The oblique pull of the muscles can be resolved into two forces, one in the axis of the rib and the other at right angles to the rib. Assuming that the angle made with both ribs is the same, the pull at right angles to the rib must be the same, as the tension at each end of the muscle is identical. The distance C D is greater than A B, hence the turning moment of the lower rib upwards is

greater than the turning moment of the upper rib downwards. The integrated result of all the fibres of the external intercostal muscles is to cause an elevation of the ribs. At the same time the muscles of the neck hold up the upper ribs and they may even raise these ribs. During the raising of the ribs the costal cartilages are twisted so that when the muscles relax the torsion of the ribs helps gravity in causing the ribs to return to the position of expiration.

With forced respiratory movements other muscles are called into action. More muscles aid the inspiratory movement, and the expiratory movement instead of being merely passively due to gravity and the untwisting of the costal cartilages is aided by

muscular action. The mechanism of the internal intercostal muscles is similar to that of the external intercostal muscles, only the excess pull is downwards because of the direction of the fibres downwards and backwards. The upper end is therefore at the greater distance from the axis, therefore the turning moment is greater downwards. During violent respiratory movements any muscle which can pull on the thorax is active.

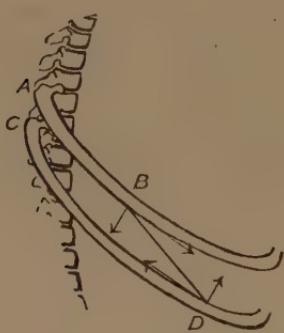


FIG. 41.—Diagram of Action of External Intercostal Muscles.

The muscle  $B\ D$  pulls equally on the two ribs. The pull can be resolved into components along the ribs and at right angles to the ribs. The equal forces at right angles to the ribs are represented by arrows of equal length. The turning moment downwards around  $A$  is less than that upwards around  $C$  because distance  $CD$  is greater than  $AB$  and the forces at  $B$  and  $D$  are equal but in opposite directions. Therefore the ribs move upwards and outwards.

causes the dome to be flattened so that the abdominal organs are pushed downwards. This produces an increase in the length of the thorax so that the three diameters ventro-dorsal, lateral and from above downwards are all increased.

The pushing down of the abdominal organs is possible only by the expansion of the sides and front of the abdomen as the pelvis and vertebral column limit expansion downwards and behind. Expansion of the sides and front of the abdomen increases the tension in its muscles in these regions so that when the diaphragm relaxes the abdominal organs are forced back to their original position. During forced expirations contraction of the abdominal muscles by increasing the pressure in the abdomen will force the

**Movements of Diaphragm.** The abdominal end of the thorax is closed by a layer of muscle with a central tendon forming the diaphragm. The muscle arises from the vertebræ, the margin of the lower ribs, and the costal cartilages. The pressure of the abdominal organs forces the diaphragm up towards the thorax in the form of a dome. Contraction of the diaphragm

liver, stomach, and spleen further up so that the diaphragm rises higher into the chest. Conversely any increase in the size of the abdominal organs will tend to limit the downward excursion of the diaphragm as in pregnancy and in cases with ovarian cysts.

**Movements of Lungs.** The increase in volume of the chest causes air to enter the chest. The mechanics of this is as follows :

The mouth and nose communicate through the pharynx and larynx with the trachea. The trachea branches and subdivides to form bronchi and ultimately bronchioles. The bronchioles open into the air sacs known as atria or infundibula, the walls of which are sacculated to form alveoli. These air spaces are the true expansile portions of the lungs which really consist of innumerable small bellows. The walls of the alveoli consist of pavement epithelial cells, blood-vessels and elastic tissue. The elastic tissue in the lungs causes a continuous inward pull in the thorax. This can be demonstrated by opening the chest wall when the lungs contract to a smaller volume than the cavity of the thorax. So long as the chest wall is closed the lungs are prevented from collapsing by the pressure of the air in the trachea which keeps the two layers of the pleuræ in contact. Separation of the two layers can take place only after puncture of the pleuræ because separation would otherwise produce a vacuum ; thus the pressure of the air keeps the lungs distended to fill the pleural sacs.<sup>1</sup>

That the pressure in the pleuræ is less than that in the lungs can be shown by inserting a tube into the pleural cavity, and also by putting one into some of the larger air tubes. By means of a manometer these pressures are measured. The difference between the intrapulmonary and intrapleural pressure is from 6 to 8 mm. of mercury at the end of expiration. The intrapulmonary pressures depart but slightly from the atmospheric pressure during quiet respiration. This is so because the viscosity of air is slight, and the air passages fairly wide. The intrapulmonary pressures are less than 1 to 2 mm. of mercury below atmospheric pressure. The difference in pressure may be observed by breathing through a wide tube with a slightly narrowed opening, the tube being connected to a manometer.

Wide variations in intrapulmonary pressure can take place when



FIG. 42.—Diagram to show the Change in Volume of the Lung Alveoli during Respiration (Roaf, *Biological Chemistry*, Methuen & Co.).

The dotted outline shows the extent of the air sac when the lung is distended.

<sup>1</sup> The lungs collapse only after a large hole has been made. When a small hole is made the adhesion of the two layers of pleuræ may keep the lung from collapsing.

one attempts to blow air into a closed space or to suck air out of a closed space. Pressures from 90 mm. of mercury above atmospheric pressure to 60 mm. below may be observed.

The intrapleural pressures vary with the intrapulmonary, being always somewhat less because of the elastic tension of the lung tissue. During inspiration the lungs expand, with the result that the elastic tissue is stretched further, and a greater difference between intrapulmonary and intrathoracic pressure is observed, and this difference may amount to 30 mm. of mercury.

The other structures in the thorax (heart and blood-vessels) are pulled on by the same elastic tension as the pleuræ, so the intrapleural pressure practically corresponds with the general intrathoracic pressure.

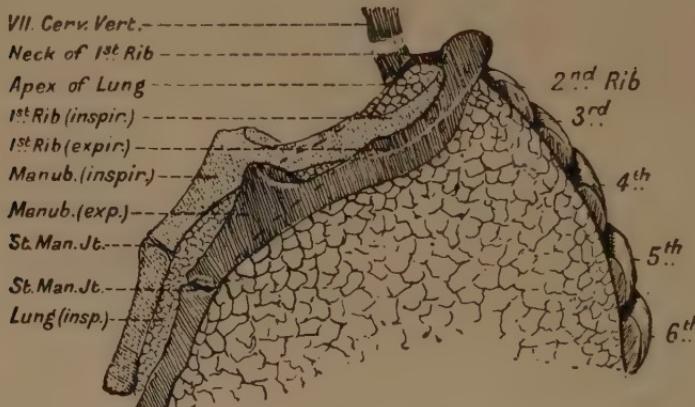


FIG. 43.—Diagram to show Respiratory Movements of the First Pair of Ribs and Manubrium Sterni and the Effect of these Movements on the Expansion of the Apex of the Lung (Keith).

Note that the lung expands horizontally in relation to the ribs.

The different portions of the lungs vary in the extent of their expansion. The central parts consisting of large bronchi, blood-vessels and nerves is inextensible; the surface layers consisting mainly of air sacs are extremely distensible; the intermediate portions are moderately distensible.

The movements of the lungs are of two kinds, corresponding to the upper and lower portions or to costal and diaphragmatic breathing respectively.

The movements of the ribs and sternum (thoracic operculum), cause an enlargement of the upper part of the thorax. The lungs remain in relation to the ribs as shown by grooves on their surface and deposit of pigment in horizontal bands. Thus there is little friction between the two pleural surfaces at the upper part of the thorax.

The movement of the diaphragm downwards causes a piston-like action so that the lower lobe extends downwards, sliding over the lower ribs. Thus there are no grooves in relation to the ribs and any pigment present is not arranged in bands. This movement over the ribs is the reason why friction "rubs" are heard more frequently in relation to the lower than the upper lobe.

**Artificial Respiration.** Respiration may be maintained in animals by rhythmical distension of the lungs with air. The rhythmical movements are not necessary if a continuous current of air can be made to pass through the lungs.

Hooke in 1667 demonstrated that an anaesthetized dog can be kept alive by a continuous pressure of air if the lungs are punctured so that the air escapes from the punctures. The air was forced in by the trachea and passed out through the punctures in the lungs. A similar method is used for operations on the thorax and upper abdomen as the respiratory movements interfere with operative procedures. A tube passed down the trachea to its bifurcation can supply a continuous current of air. The lungs are kept distended by the pressure of the air as the size of the tube is so adjusted that the air cannot escape too easily between the catheter and the wall of the trachea.

When respiration has ceased in the human being life may be

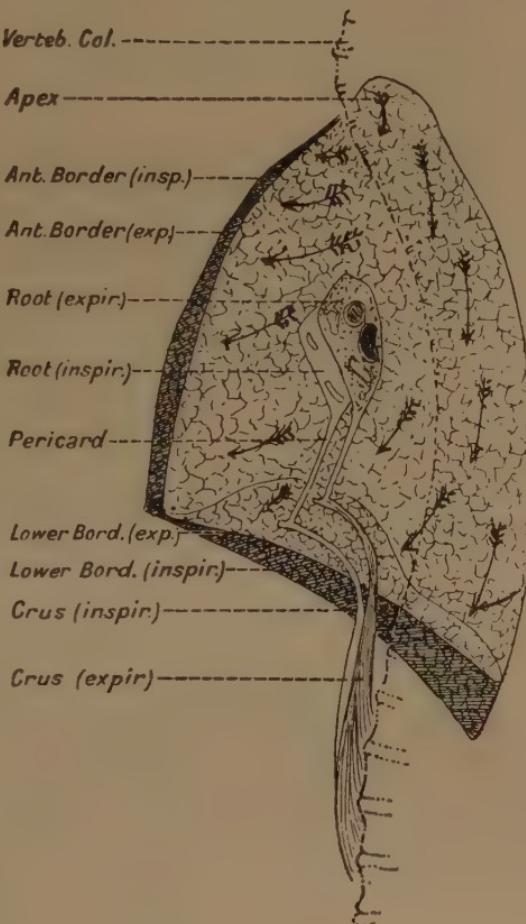


FIG. 44.—Diagram to show the Respiratory Movement of the Root of the Right Lung (Keith).

The mediastinal aspect is shown. Note that the posterior lobe of the lung expands vertically, sliding over the ribs.

When respiration has ceased in the human being life may be

saved by artificial respiration. The best method of doing this is Schafer's method.

This method depends on the elasticity of the thorax. The resting position is that of expiration and the person to be restored is placed face downwards with a pad under the upper part of the chest. This position has the advantage that it prevents the tongue from falling back to close the pharynx, and any liquids can easily flow out of the mouth (this is especially important in cases of drowning). The operator places both hands on the sides of the lower



FIG. 45.—Schafer's Method of Artificial Respiration (from Rowland's *Hygiene for Teachers*).

part of the thorax and keeping his arms stiff he swings forwards and backwards at the rate of about sixteen times per minute. The rhythmical compression forces air out and on relaxing the pressure air is sucked in by the elasticity of the thorax. The rhythmic compression also aids the circulation. Artificial respiration may be carried out in children by placing a handkerchief over the mouth and blowing into the mouth. A hand on the abdomen prevents distension of the stomach with the air.

NOTE.—For further information the student should consult A. Keith, "The Mechanism of Respiration in Man," in *Further Advances in Physiology*, edited by L. Hill, 1909 (Edward Arnold & Co.).

## CHAPTER V

### MECHANICS OF THE CIRCULATION: THE HEART

The pulsations of the blood-vessels can be felt at various places and they may sometimes be seen, notably in the neck (see Fig. 58, p. 78). These pulsations are due to the action of the heart in forcing blood into the arteries. The problems of the circulation can be described under two headings : (1) those concerned with the heart acting as a pump and (2) those concerned with the flow of blood in the blood-vessels.

#### The Heart

The heart is a hollow organ composed of a special type of muscle, cardiac muscle. Surrounding the heart is a strong fibrous sac called the pericardium. The interior of the heart and the two surfaces of contact between the heart and the pericardial sac are all three covered by pavement cells.

When the heart contracts the muscle exerts a pressure on its contents. The contents are forced out into the blood-vessels and the heart diminishes in volume. This diminution in volume is accompanied by a change in shape. If it were not for the two smooth layers, the covering of the heart and the lining of the pericardium, with some lubricating fluid between them, the change of shape would cause pulling on neighbouring structures. Owing to the arrangement described above the heart moves easily in the pericardium without hindrance from the fixed structures near it.

The properties of heart muscle differ in certain characteristics from striated muscle. For example when the heart of an animal is exposed it is seen to contract rhythmically ; skeletal muscles on the other hand contract only in response to impulses reaching them either directly or through the nerves. As the heart may continue to beat when removed from the body it is obvious that these rhythmical contractions may occur independently of the nervous system.

**Properties of Heart Muscle.** Many of the phenomena of heart muscle can be demonstrated on frog's heart muscle. The movements can be measured in two ways.

(1) The first method is to use a lever attached by means of a thread to the heart muscle. When the heart muscle contracts it shortens and pulls on the lever. The movements of the lever can be recorded on a moving surface. In the case of a small muscle such as the heart of the frog the lever must be delicately balanced so that the heart has not much initial load on it. This is accomplished either by balancing the lever by a counterpoise on the opposite side of the axis or by suspending the lever from a light spring. In the latter case the varying tension of the heart merely puts more or less tension on the spring and the lever moves up and down as the spring shortens or stretches.

With such slight variations in pressure it is important to diminish the friction of the writing point on the recording surface. The best writing point is that devised by Sherrington. It consists of a light capillary glass tube pivoted in a straw; the right-angled bend causes the writing point to lie in front of

the lever. When pressed against the writing surface the capillary swings backwards and does not cause much friction. Before inserting the lever into the split end of the straw the inner end may be bent as shown in Fig. 46, so as to cause the writing point to swing further forwards.

Another form of writing point consists of two pieces of parchment paper united by a hinge of peritoneal membrane.

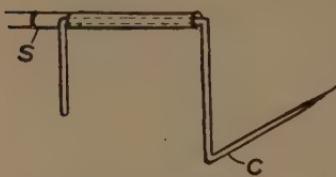
FIG. 46.—Sherrington's Frictionless Writing Point.

A small glass capillary *C* lies in the end of a split straw *S*. The writing point presses against the drum only by its weight.

tonement membrane. The hinge allows the writing point to be against the writing surface, but the pressure is very slight and even (Bayliss).

(2) The second method of studying the contraction of the heart is to place the heart in a vessel with rigid walls and to measure the changes in volume of the heart and its contents. The mouth of the rigid box is closed by a rubber membrane through which the ventricles fit. The cardiometer is connected to a recording apparatus. The one shown in Fig. 47 is a metal box floating on water. The box rises and falls with the changes in volume of the heart. The change in volume is due to the passage of blood through the heart. In other words the cardiometer measures the output of the heart. The part of the apparatus to the left is used to regulate the resistance against which the heart works. A tube dips into mercury and the depth to which it dips determines the pressure at which the blood escapes.

By means of stimuli sent into the heart at varying intervals



during its contraction it can be shown that heart muscle has a relatively long refractory period. In the case of striated muscle (see p. 31) the refractory period corresponds to the latent period. In the case of the heart the muscle is irresponsive during the greater part of its contraction. One result of this condition is that the heart cannot be tetanized as it always commences to relax before another contraction takes place.

If stimuli are sent in early in the contraction they may produce an *extra contraction* but the latent period is very long. This is well shown in Fig. 48, in which the latent period is shaded. It will be noticed that the extra contraction is followed by a long *compensatory pause* so that the subsequent contraction occurs at the same time interval that it would have done if the extra contraction had been at the normal time. In other words the normal rhythm is regained by a pause when an extra contraction occurs soon after a normal contraction.

The *refractory period* can be divided into two parts, absolute and relative. During the former the heart cannot be excited by a stimulus however strong it may be. During the latter the heart will respond but it requires a stronger stimulus than usual. The excitability increases rapidly from zero to its normal value.

Relative and absolute refractory periods and the prolonged latent period to a second stimulus can be shown in other tissues.

The result of a change of temperature is similar to that on skeletal muscle, but as the heart is beating rhythmically a rise in temperature produces a more frequent beat.

When we wish to study the contraction of heart muscle in response to artificial stimuli we must obtain a preparation in which the heart is quiescent. This can be accomplished in the frog by tying a ligature round the heart between the sinus venosus and right auricle. To arrange this ligature lift up the apex of the heart and pass a thread, caudal to the arteries, and cephalic to the veins. Turn the ends of the thread caudalwards to meet round the venous portion of the heart and tie it round the junction of the sinus venosus with the auricle. This ligature stops the beat of the auricle and ventricle (First Stannius ligature); the cause of the stoppage will

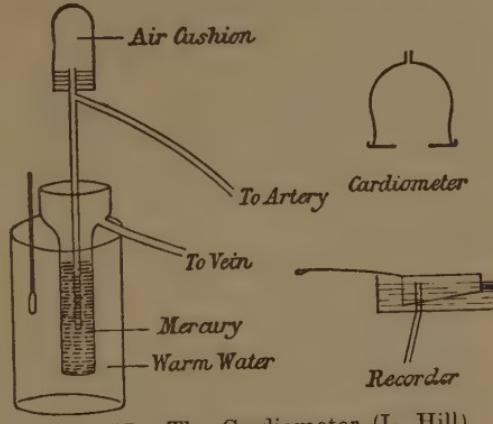


FIG. 47.—The Cardiometer (L. Hill).

be discussed later (see p. 71). Such a quiescent heart may be stimulated and its contraction recorded in the same way as with skeletal muscle. Most of the phenomena of contraction are the same as those shown in skeletal muscle. The improvement in contraction with the first two or three stimuli is usually well marked ; this is called "*staircase phenomenon*" because of the steplike rise.

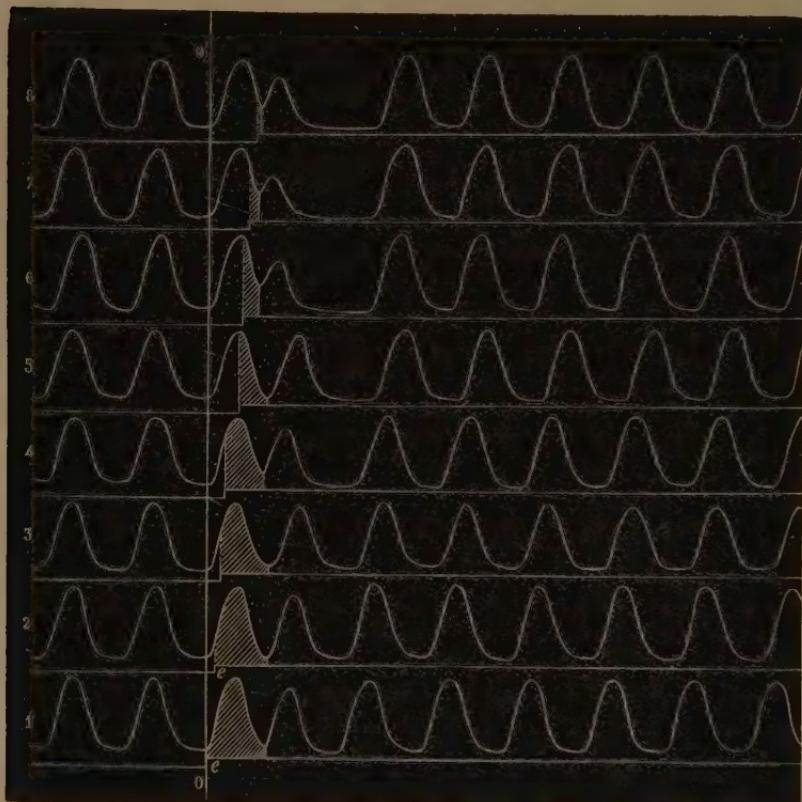


FIG. 48.—Electrical Stimulation of Warmed Frog's Heart to show the Effect of Stimuli at different Time Intervals in relation to the Cardiac Cycle (Marey).

The earlier the stimulus occurs in the systole the longer the latent period, as shown by the shaded areas. The extra contraction is followed by a compensatory pause. Heating the heart causes the refractory period to become shorter, otherwise no extra contraction would follow the earlier stimuli, e.g. those shown in tracings 1, 2, 3 and 4. Read from left to right.

The contraction of the heart is slower and the refractory period is longer than in skeletal muscle.

The most distinctive difference between cardiac and striated muscle is that the contraction of the heart does not vary in extent with the variation in strength of the stimulus. This is called the "*all or nothing*" law. The difference between these two kinds of

muscle is, however, due to the anatomical arrangement of fibres and not to a fundamental difference in the nature of the tissue. The fibres of cardiac muscle are branched and communicate with each other by intercellular bridges, therefore a stimulus affecting one part of the heart spreads to all parts of the same. Further the ventricle of the mammalian heart is supplied with a special conducting system of Purkinje fibres which convey an impulse to all parts of the ventricle at almost the same instant.

The fibres of skeletal muscle consist of cylinders which do not communicate with each other: therefore when stimulated by a weak stimulus only a few fibres in contact with the electrodes contract. With stronger stimuli the excitation affects more and more fibres of the muscle, hence greater contraction with stronger stimuli. The same holds good when the muscle is stimulated through its nerve. The density of the current is greatest close to the stimulating electrodes. With weak electric currents only those fibres which are close to the electrodes are stimulated. With stronger currents the current density increases so that some of the outlying fibres are stimulated in addition to those close to the electrodes.

**Cardiac Cycle.** As the heart muscle contracts it presses on the blood contained in its cavity. When the pressure becomes greater than that in a neighbouring cavity the blood is squeezed out. - The contraction of the heart muscle is isometric whilst the pressure is rising—i.e. the muscle cannot shorten whilst the cavity is full of blood, but it produces increasing tension. When the heart is being emptied the contraction is isotonic, i.e. the muscle shortens without much increase in pressure.

The direction of the blood flow depends upon the presence of valves. Between auricles and ventricles are the auriculo-ventricular valves which consist of thin membranous flaps. On the right side there are three flaps (tricuspid) and on the left two flaps (mitral valve). These flaps are turned towards the ventricle and they are held in place by minute tendons (chordæ tendineæ). The tendons are attached to the tips of projections of the heart muscle called papillary muscles. By the action of these valves whenever the pressure in an auricle is greater than in the corresponding ventricle the blood can flow over the smooth surface of the valve into the ventricle, but whenever the pressure in the ventricle is greater than that in the auricle the edges of the valves are pressed together so that the opening is closed. The valves are prevented from being forced back into the auricle by the chordæ tendineæ, and the shortening of the ventricle as it contracts is compensated by the contraction of the papillary projections. In other words the chordæ tendineæ, are kept taut although the distance from the valve to the apex of the heart has been decreased.

The openings from the ventricles to the arteries are furnished with three membranous pockets (semilunar valves). When the pressure in the ventricles is greater than that in the arteries the blood forces these pockets towards the vessel wall so that blood flows freely into the artery. When the pressure in the ventricle falls below that in the artery the pockets fill and bulge inwards so that they meet forming an efficient barrier to prevent blood from flowing back into the ventricle.

The ordered sequence of contraction favours the movement of blood through the heart. Blood flows into the auricles and ventricles from the veins. Suddenly the auricles contract forcing their contents into the ventricles. Almost immediately afterwards the ventricles contract forcing the blood into the pulmonary artery and aorta respectively.

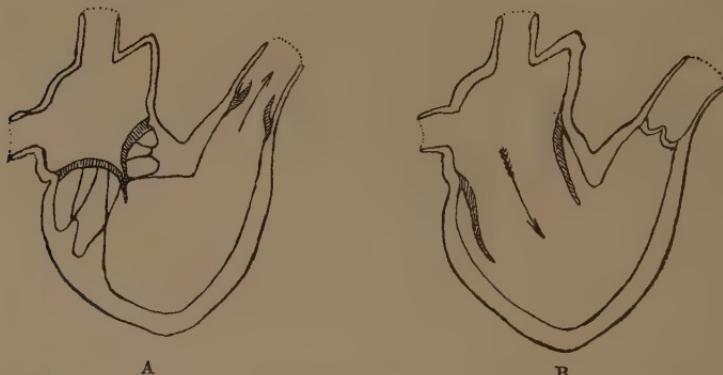


FIG. 49.—Diagram of Right Side of Heart (Leonard Hill).

A = during systole. A-V, valves shut and chordae tendineæ drawn taut, semilunar valves open and blood flowing into pulmonary artery.

B = during diastole. A-V, valves open, blood flowing in from auricle, semilunar valves shut.

The contraction of the auricles tends to distend the ventricles, thus putting their fibres on the stretch. This stretching has a distinct mechanical advantage. Although muscle does not obey Hooke's law we know that in order to stretch a contracted muscle to the same length as a resting muscle, a greater pull must be exerted on the contracted than on the uncontracted muscle (except when the weight is too great to be lifted, see p. 24). Therefore a stretched muscle, when it passes into the new pseudo-elastic state of contraction, will exert a greater tension than one not stretched. This has been called the Law of the Heart (Starling). It is really a property common to all elastic structures. The sequence of events has been studied in various ways in animals and the same cycle can be demonstrated in man. The elementary observations may be made by sight and touch.

When Harvey (1628) first commenced to study the circulation he said: "I was almost tempted to think, with Fracastorius, that the motion of the heart was only to be comprehended by God." Yet he was able to prove by a series of experiments and cogent arguments that the blood does circulate.

If the slowly beating heart of a cold-blooded animal is watched it will be seen that the beat commences at the venous and ends at the arterial end. Thus, in the frog, it can be seen that the beat passes over sinus, auricle, ventricle in that order. In the mammal the order is auricle to ventricle. The frog's heart is permeated with blood, hence it is seen to become pale when it contracts and the blood is squeezed out of the interstices. The relaxed heart is soft and flabby, but the contracted heart can be felt to be firm and hard like any other contracting muscle. It is comparatively easy nowadays to prove that the blood circulates because of the experimental methods which have been developed. One of the most important of these methods is the measurement of pressures in the various compartments associated with the heart.

**Intracardiac and Arterial Pressures.** The original method of Chauveau and Marey (1863) was to pass a tube (sound) down the jugular vein or carotid artery of a horse into the heart. On the end of the tube was a small bag. The bag and tube were filled with liquid and connected to some form of recording apparatus. Various improvements have been made in the methods of recording (see Fig. 54, p. 74), but the methods are essentially the same. The blood in the heart presses on the bag, and this pressure is communicated through the liquid in the tube to the recording apparatus.

By using a sound composed of two tubes, one of which is slightly longer than the other, the pressures in an auricle and a ventricle can be recorded simultaneously. A comparison of the pressure records obtained from the heart cavities and the arteries coming from the heart agree in all respects with what one would expect from the anatomical arrangement of the parts. Normally both sides of the heart contract at the same time, and therefore one description will serve for both.

*Auricular Systole.* Starting with the resting condition of the heart the blood will flow directly from the veins into both auricles and ventricles. The heart beat commences by the contraction of the auricles. This contraction commences at the large veins and spreads over the auricles. The result of this mode of contraction is that the veins are largely closed off and the blood in the auricles is propelled towards the ventricles. There is not so much a rise in pressure in the auricles as an onward movement of the blood towards the ventricles. As the pressure in the auricles is low

it is recorded in terms of water pressure. This onward movement of the blood produces a rise in pressure in the ventricles (see p. 77), and the auriculo-ventricular valves close, thus preventing regurgitation into the auricle. The eddy currents produced by the flow of blood through the constriction formed by the auriculo-ventricular opening will push the valve flaps away from the ventricular wall so that they are in the correct position for closing.

#### Ventricular Systole.

Immediately after the contraction of the auricles the ventricles contract. The initial stage of their contraction is isometric, the cavity being closed. When the pressure rises to that in the aorta and pulmonary artery respectively the semilunar valves open. The rest of the contraction is isotonic as the heart muscle shortens and the pressure rises only slightly. During the emptying of the ventricles the pressure is almost the same as that in the large arteries, but there must be a slight excess of pressure in the

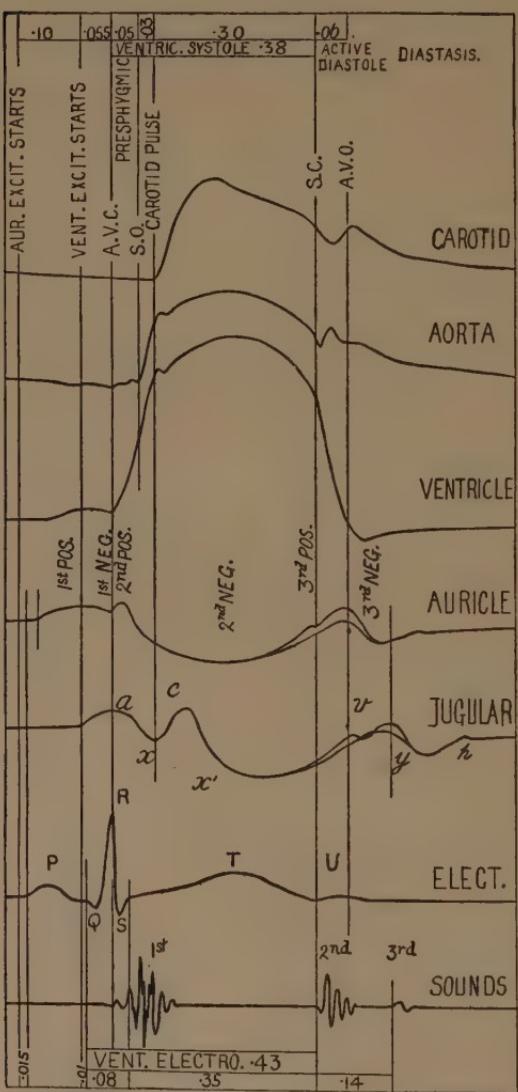


FIG. 50.—Pressure and Electrical Changes and Heart Sounds in their relation to the Cardiac Cycle (T. Lewis).

ventricles to account for the onward movement of the blood. As the large vessels become distended with blood the pressures must rise slightly. Finally the ventricles relax and the semi-

lunar valves close, thus preventing regurgitation of blood into the ventricles.

*Cardiac Impulse.* During contraction the ventricle becomes hard. As the ventricle is lying close to the anterior wall of the thorax this hardening can be felt and seen through the intercostal spaces.

The cardiac impulse may be partly due to pressure of the heart against the chest wall. Additional pressure in the aorta during systole will tend to cause the arch to open out, thus pushing the heart forward.

If the button of a Marey's tambour be pressed in an intercostal space it will be forced outwards with each contraction. The button is usually placed near the apex of the heart, and the record can be made by a recording tambour. The apex of the heart is usually behind the fifth intercostal space about  $3\frac{1}{2}$  inches from the middle line. It varies in position in different individuals and in the same individual in different attitudes.

*Auricular Diastole.* After the auricles have contracted they remain quiescent and blood flows into them from the veins. As the blood enters, the pressure rises in the auricles. Part of this rise of pressure may be due to bulging of the auriculo-ventricular valves into the auricles (the "C" wave of the polygram may be in part due to this). When the ventricles relax the auriculo-ventricular valves open and blood flows into the ventricle. This flowing away of blood causes a fall of pressure, but as the ventricles become filled the continuous flow of blood from the veins causes a gradual rise of pressure (V or "venous stasis" wave) in both auricles and ventricles.

*Ventricular Diastole.* When the ventricles relax the semi-lunar valves close and the auriculo-ventricular valves open. Blood flows from the auricles gradually filling the ventricles.

**Time Relations of the Heart Beat.** The average frequency of the heart beat in an adult man varies with his position. When lying down the frequency is about 60 per minute, when sitting it is 72 per minute, and on standing up the frequency is usually about 75 per minute. Thus each beat lasts 0.8 of a second, which can be conveniently divided into periods of 0.1 of a second.

The auricular systole lasts 0.15 of a second, therefore the auricular diastole lasts 0.65 of a second. The ventricular systole lasts 0.35 and its diastole 0.45 of a second. As the ventricular systole follows the auricular systole the total systole of auricles and ventricles is 0.5 of a second, and both of them are synchronously at rest for 0.3 of a second. The diastole of the auricle overlaps the systole of the ventricle for 0.35 and the diastole of the ventricle overlaps the systole of the auricle for 0.15 of a second. Associated

with the heart beat are certain sounds and changes in electrical potential.

**Heart Sounds.** On listening to the beating heart two sounds may be distinguished, one low and rumbling, the other high and concise. The first of these corresponds to the early stage of contraction of the ventricle. It is produced by the closure of the auriculo-ventricular valves and the vibrations of the contracting muscle. The second sound corresponds to the relaxation of the ventricles and it is due to the closure of the semilunar valves. The pitch is higher because the valves are smaller than the auriculo-ventricular-cusps, and the arterial pressure is high.

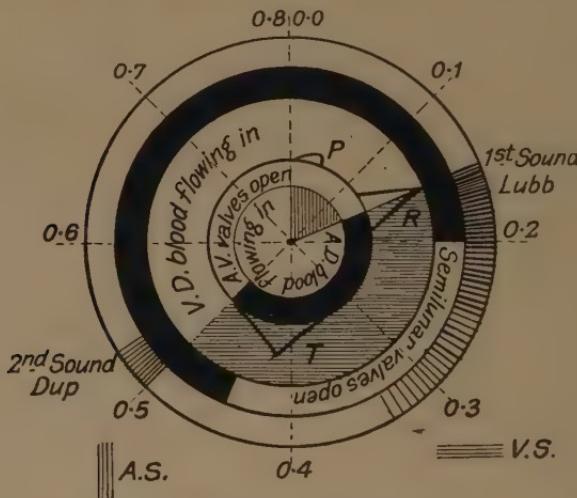


FIG. 51.—Composite Diagram showing the Events of the Cardiac Cycle.

The inner circle shows auricular systole and diastole. The ring next to the inner circle shows the auriculo-ventricular valves. The second ring shows the systole and diastole of the ventricle, and outside this is the ring representing the semilunar valves. The heart sounds are shown in the outermost ring. The clear spaces show the blood flow. Blood flows into the auricle during diastole and through the auriculo-ventricular valves into the ventricles during the diastole of the ventricle. Blood flows from the ventricles into the arteries during that part of ventricular systole when the ventricular pressure exceeds that in the arteries.

The *P*, *R* and *T* waves of the electrocardiogram are shown in the ring representing the ventricular systole and diastole. Time intervals from Lewis (compare with Fig. 50).

As there are two auricles and two ventricles these sounds are each double, and if the two sides of the heart are not beating synchronously the difference in time may be detected by the duplication of the heart sounds.

The above explanation is based on simultaneous records of the heart beat and the heart sounds. By means of a microphone the sounds can be recorded electrically.

These records show the coincidence of the heart sounds with the phases of the heart beat. Experimental investigation shows that if the valves are hooked back the normal sounds are altered, thus

showing the valvular element in the sounds. As the first sound is still faintly heard in an excised bloodless heart it is probably partly due to the contraction of the ventricular muscle. Similar sounds may be heard over contracting striated muscle.

The sounds are due to vibrations which set up air vibrations at the surface of the chest. Different vibrations will be produced by eddy currents in the blood. If by reason of disease the valves do not open properly so that the blood has to flow through a narrow orifice, the vibrations set up will precede the normal valvular sound. Such a blowing sound produced by stenosis of the auriculo-ventricular valves will occur before systole, and it is said to be a *pre-*

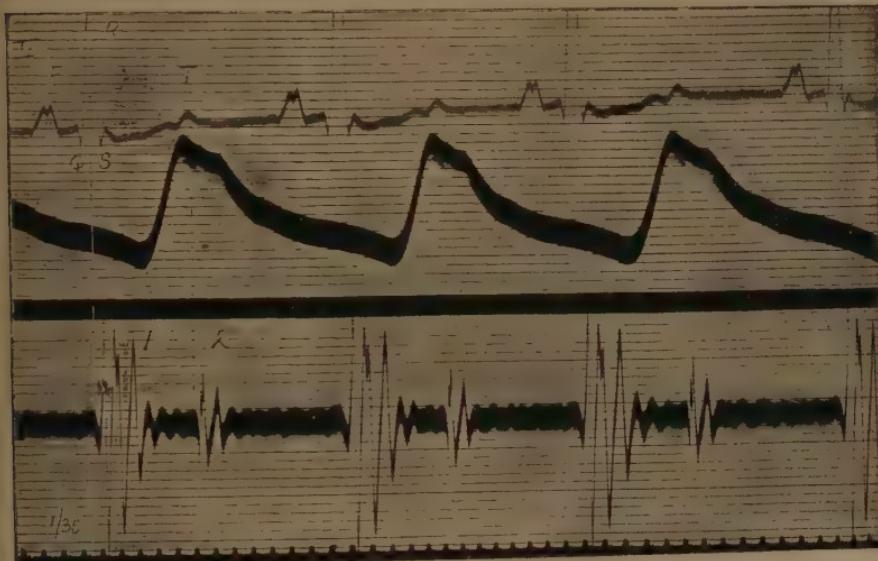


FIG. 52.—Electrocardiogram, Carotid Pulse Record and Electrical Record of Heart Sounds (T. Lewis in *Q'yly. Jnl. of Medicine*).

The sounds are recorded by a microphone connected to a second string galvanometer. 1 = first sound; 2 = second sound. Time marking in  $\frac{1}{30}$  secs.

*systolic murmur.* When the semilunar valves fail to open to their full extent the blowing sound will occur towards the end of systole. There will therefore be a *systolic murmur*.

Incompetence of the valves so that they do not close properly allows regurgitation of the blood with a rushing sound. Incompetence of the auriculo-ventricular valves causes a murmur at the commencement of systole and incompetence of the semilunar valves causes a murmur at the commencement of diastole. These are called *systolic* and *diastolic* murmurs respectively. The opening at which the murmur originates is determined by the position where the murmur is heard most distinctly. Murmurs at the tricuspid valve are best heard at the apex of the heart. Those at

the mitral valve are loudest on the right near the cartilage of the seventh rib, whilst the pulmonary and aortic murmurs are listened for at the second intercostal space on the left and right sides respectively.

**Electrical Changes during the Cardiac Cycle.** The heart is a muscle, hence its contraction is accompanied by changes in electrical potential.

These may be recorded as in the example in Fig. 28 where the electrodes were placed directly on the beating heart of a toad. Potential differences will spread from the heart to the body surface. As shown in Fig. 53 the equipotential lines reach the body surface asymmetrically because of the oblique lie of the heart. The methods of recording the electrical potentials are so delicate that the records can be made from the body surface. The electrodes can be connected to various parts of the body, but three standard combinations are used in practice namely :—



FIG. 53.

A and B represent the positions of greatest cardiac potential difference. Any difference of potential between A and B will cause a current. The axis of maximum potential difference will be along the line CC and the line OO represents the plane of zero potential. The lines *a a a . . .* and *b b b . . .* represent sections of equipotential surfaces around A and B. Any leads on opposite sides of the plane OO will show differences of potential. The variations in the electrocardiogram with different leads suggests that the axis *cc* is not the same for each variation in potential. The interrupted lines *cc* show course of the currents in the body (from Waller's *Human Physiology*, Longmans, Green & Co.).

Lead I from right arm to left arm.

Lead II from right arm to left leg.

Lead III from left arm to left leg.

Records made from these three leads give slightly different results as the potentials depend upon the lie of the heart in relation to the body surface. The changes in potential are believed to

represent the differences in potential between the base and the apex.

The normal record shows a small potential P wave, corresponding to the contraction of the auricles. Following this is a series of changes called the ventricular complex. The records are always made so that negative potential at the base causes a rise in the record. The ventricular impulse starts and ends with base negative waves, R and T waves. Between these there may be other potential changes such as a base positive wave S.

The heart is thus seen to be a hollow muscle, and its contraction can be studied by direct observation or by records of—

- (a) Changes in shape such as its length.
- (b) Changes in volume by the cardiometer.
- (c) Changes in pressure in its various cavities.
- (d) Changes in hardness giving rise to the cardiac impulse.
- (e) Sounds produced during the various phases of the cardiac cycle.
- (f) Changes in electrical potential.

If the experiment (First Stannius Ligature) described on p. 61 is succeeded by the tying of a ligature round the junction of the auricle and ventricle (Second Stannius Ligature), the latter usually starts to beat. The first ligature acts by inhibiting the rhythmical activity of the heart, possibly by its action on nerve cells in the region of the sino-auricular groove. Often the heart recommences, without the second ligature, within less than half an hour of the first ligature. Later on we shall find that the vagus nerve has a similar influence on the mammalian heart—namely it slows or stops its rhythmical activity. The Stannius experiment owes its influence to an action on the excitability of the neuro-muscular mechanism of the heart of the frog. At one period this experiment was of great interest because of the interpretations placed upon it with reference to the cause and maintenance of the rhythmical beat of the heart.

## CHAPTER VI

### CIRCULATION IN THE BLOOD-VESSELS

**Harvey.** The proof that the blood circulates was first furnished by Harvey in 1628. Part of that proof was the anatomical arrangement of the valves of the heart. He showed that liquid injected into the venous end of the heart could pass through to the arterial end, but not in the reverse direction. He argued that if only a small quantity of blood (half an ounce) passes through at each beat the whole blood in the body would pass through the heart in about half an hour, therefore the blood must pass back to the heart in a circle.

Another part of his proof was that when an artery is cut, blood spurts in jerks from the portion of the artery still connected with the heart, but that when a vein is cut the blood flows steadily from the portion of vein cut off from the heart. He further showed that ligatures round the vessels and round the limbs prevented the flow of blood. A tight ligature round the arm stops the pulse and stops the blood flowing in the arteries, but a loose ligature causes the arm to swell because the veins are occluded and blood accumulates by flowing in through the arteries. This shows in addition that the arteries require a greater pressure than the veins to obliterate them. He also pointed out that the general effect of poisons introduced into the blood indicates that they are distributed by some mechanism such as the flow of that liquid.

Harvey's proofs that the blood circulates are summarized as follows :

- (1) The arrangement of the valves of the heart is such that liquid can pass only in one direction.
- (2) Blood flows in spurts from the proximal end of cut arteries and as a constant stream from the distal end of cut veins. A ligature placed round the great veins near the heart prevents blood from entering it whilst a similar ligature round the aorta causes the heart to become distended with blood.
- (3) A tight ligature round the arm causes it to remain pulseless and to become cold because all the vessels are occluded by the ligature. If the ligature is somewhat relaxed the arm swells, due to the flow of blood into it by the arteries, whilst the pressure round the arm is still great enough to prevent blood from flowing out by the veins.

(4) The valves in the veins permit the flow of liquid only in one direction. If the blood is squeezed out of a vein between two valves the vein can fill up only if the distal end is opened. Provided no collateral vessel is present the length of vein remains empty so long as the distal end is kept closed.

(5) The distribution of heat to the limbs is evidence of a circulation of blood.

(6) The actions of poisons, introduced at one point of the body, on other parts is a further proof of the circulation.

It was not until after Harvey's death that Malpighi in 1661 showed the presence of capillaries. Harvey assumed that the blood passed from the arteries to the veins through the "pores" of the organs.

The study of these phenomena is primarily a consideration of the flow of liquids in tubes.

The first point is that a liquid flows from a place where the pressure is high to one where it is lower. As seen in the preceding chapter it is the function of the heart to produce a high pressure in the large arteries. Therefore measurements of pressure are an important part of the present study.

**Methods of Measurement.** The first recorded measurements of blood pressure were made by Stephen Hales (Rector of Farringdon and Minister of Teddington). The following quotation (*Statistical Essays*, Vol. II, 1733, p. i) is of interest: "In December I caused a Mare to be tied down alive on her back, she was fourteen Hands high, and about fourteen Years of Age, had a *Fistula* on her Withers, was neither very lean nor yet lusty: Having laid open the left crural Artery about three inches from her Belly, I inserted into it a brass Pipe whose Bore was one sixth of an Inch in Diameter; and to that, by means of another brass Pipe which was fitly adapted to it, I fixed a glass Tube, of nearly the same Diameter, which was nine Feet in Length: Then untying the Ligature on the Artery, the Blood rose in the Tube eight Feet three Inches perpendicular above the Level of left Ventricle of the Heart."

Although Hales had used mercurial manometers for pressure measurements in plants it was not until 1828 that Poiseuille introduced a U-tube containing mercury for experiments on animals. Now all standard measurements of arterial pressure are recorded in millimeters of mercury. In 1847 Ludwig added a float to the mercury in the U-tube and thus rendered possible the graphic recording of blood pressure.

For rapid pressure changes the mercury has this one disadvantage, that change of pressure is accompanied by movement of the mercury in the tube and the inertia due to the weight of the mercury causes the same drawbacks that were studied in relation to muscle levers.

The rise and fall of pressure is delayed and when the mercury is in movement it may continue in movement and pass the true pressure valve. To eliminate this inertia a closed system is used with a minimal volume change and this slight change is magnified in some way. The only disadvantage of all such systems is that the records of them must be standardized against measurements of pressure by means of the mercury manometer.

In 1866 Fick introduced a curved flattened hollow tube which opens out when liquid is forced into it under pressure. The movement of the C spring (Bourdon gauge) is recorded by means of a lever system. In 1888 Hürthle introduced a small tambour which moves against a spring and the movement is recorded by a lever.

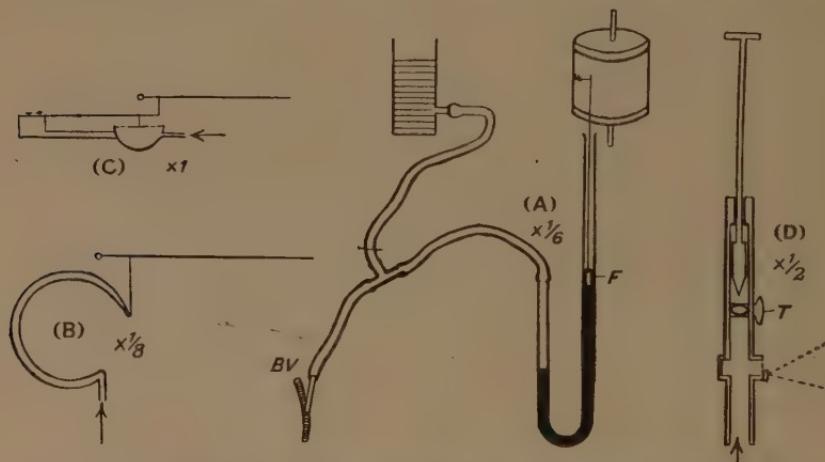


FIG. 54.—Diagram of various Methods for recording Blood Pressure.

- (A) Mercury manometer with float recording on smoked surface (Ludwig). *BV* blood-vessel into which cannula is inserted. The vessel for filling the apparatus is shown above.
- (B) C-spring manometer (Fick) with lever (Bourdon gauge).
- (C) Small tambour working against a stiff spring (Hürthle).
- (D) Tube with membrane on which a mirror rests (Piper). The plunger can close the open end of the tube. After the tube is tied on, the plunger is withdrawn and the tap *T* closed. The reflection of light is indicated by the dotted lines. Variations of pressure cause movements of the membrane which are recorded by the movement of the light (compare lower part of Fig. 10).

In 1905 Frank substituted a light mirror for the lever and recorded the movement by reflection of a beam of light on to a photographic recording surface. The maximum and minimum pressures can be measured by mercury manometers with valves to permit movement of liquid only in one direction.

In animals the pressure is recorded by inserting a cannula into a blood-vessel and connecting the pressure recorder to the cannula by means of stout-walled pressure tubing, but for measurements of pressure in the human subject another method is adopted.

If an elastic tube is pressed on from the outside its lumen can be obliterated and the pressure required to obliterate it is greater than

higher the pressure inside the tube. This is the foundation of the method for measuring arterial pressure in man. The pressure recorder is attached to an elastic bag which is placed over an artery and held in place by an inextensible covering. Air is pumped into the bag until the pulse ceases beyond the area of constriction. This gives the pressure required to obliterate the pulse. By allowing the pressure to fall we find the pressure at which the pulse reappears beyond the constriction. The mean of these two is the value for the maximum pressure in the artery. The true pressure must be slightly less than this because a small portion of the pressure must be used up in overcoming the elasticity of the vessel wall and in deforming the tissues during the process. However, measurements on animals show that the pressures recorded by the "Armlet" method are almost the same as those made by connecting the artery directly to the pressure-measuring apparatus.

*Methods for Measuring Velocity of Flow.* Before leaving the subject of pressure measurements it is necessary to point out that in addition to the pressure of the blood in the artery there is another force to be measured which is erroneously spoken of as the velocity pressure. This is not a pressure because it is the kinetic energy due to the forward movement of the blood. It may be measured by the height of liquid that the kinetic energy can support, hence it is often spoken of as a pressure. To measure the force of the kinetic energy one may cause the moving blood to flow against a plate and measure the deflection of the plate against the tension of a spring, and from the deflection of the plate the rate of flow can be deduced. This is exemplified by Chauveau's Hæmodromograph.

The average velocity of flow can be determined by measuring the volume flowing out in a given time and dividing the amount by the area of the tube from which the liquid flows.

Another method of measuring the kinetic energy of flow is a modification of Pitot's tube. To measure the velocity of wind a large tube is arranged so that it points in the direction of the air

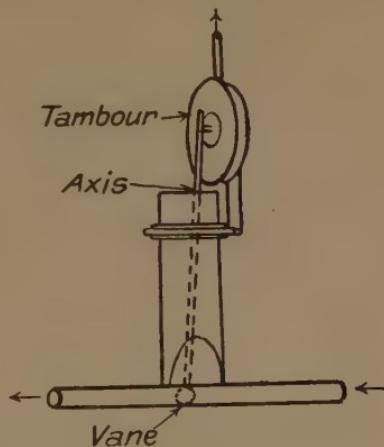


FIG. 55.—Chauveau's Hæmodromograph.

A current of liquid through the lower tube in the direction of the arrows presses on the vane. The long handle is pivoted at the top of the wide tube so that the far end of the handle presses on the tambour which drives air out in the direction of the arrow. The pressure is recorded by a recording tambour and the instrument can be standardized to show the velocity of the liquid for any given movement of the tambour.

To measure the force of the kinetic energy one may cause the moving blood to flow against a plate and measure the deflection of the plate against the tension of a spring, and from the deflection of the plate the rate of flow can be deduced. This is exemplified by Chauveau's Hæmodromograph.

movement. Two bent tubes are inserted into the large tube so that the wind blows down one, causing a pressure, and draws air out of the other, causing a suction. The two bent tubes are connected below by a U tube with water in it. From the difference in level of the water the velocity of the wind may be calculated.

To adapt this principle to the measurement of the velocity of blood flow the two bent tubes instead of being united by a U tube may be united to the two ends of a cylinder with a piston in between. This piston will move by the differences in pressure and by making it move against a spring the difference in pressure can be measured.

Another way in which to measure the kinetic energy is to use a D-shaped tube. As shown in Fig. 56 (B), the liquid enters at the

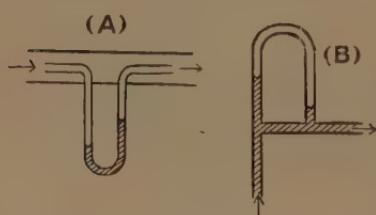


FIG. 56.—(A) Pitot Tube for Measuring Velocity of Wind.

Air blowing in the direction of the arrows causes pressure on one limb of the U-tube and suction on the other one. The result is a displacement of the liquid in the U-tube.

(B) Adaptation of above to measure Velocity of Blood Flow.

The pressure on the surfaces of liquid in the two upright tubes is the same as they are connected by a closed tube containing gas. The momentum of the liquid entering the upright tube on the left forces the liquid up that tube and presses down the liquid in the other upright tube. The difference in level is a measure of the velocity of flow.

the velocity of blood flow.

The various factors which govern the amount of liquid flowing through a tube are related by Poiseuille's formula, which is

$$\frac{\text{Volume}}{\text{time}} = \frac{(p_1 - p_2) \pi r^4}{8l\eta}$$

in which  $p_1 - p_2$  is the difference in pressure at the two ends of the length  $l$ ,  $r$  is the radius of the tube and  $\eta$  is the coefficient of viscosity. As velocity is determined by dividing the volume passed through in a given time by the area of the tube we can write down the formula for velocity as—

$$\text{Velocity of flow} = \frac{(p_1 - p_2) r^2}{8l\eta}.$$

upright line of the D and flows out along the horizontal line. If there is no movement of the liquid any pressure in the liquid will compress the gas in the upper part and the liquid in the two tubes will stand at the same height. When the liquid is flowing the kinetic energy of flow will cause it to run up the first tube. As the pressure in the gas is transmitted equally to both tubes the liquid in the opposite limb will be forced downwards. The difference in height in the two tubes measures the kinetic energy of the flow of the liquid. Cybulski photographed the height of liquid in the two tubes, thus measuring

As the blood-vessels are tubular these equations express the various factors to be studied in relation to the blood flow. The measurement of pressure has been described above and the importance of blood pressure measurement is indicated by Poiseuille's equation.

There is an additional theorem to be described. Bernoulli's Law states that in a given system of flowing liquid the total energy is a constant. This can be written in the form—

$$gph + P + \frac{1}{2}\rho v^2 = \text{a constant.}$$

The first term represents the potential energy due to position,  $g$  = gravity constant,  $\rho$  = density, and  $h$  is the height above sea level.  $P$  = lateral pressure on the containing walls and  $\frac{1}{2}\rho v^2$  is the kinetic energy due to the onward flow. The measurement of the kinetic energy has been described above. The effect of gravity will be shown in the difference in pressure between the blood in the head and lower limb in the standing position.

It is true that the energy is being dissipated whilst the blood is flowing. Friction against the walls converts some of the energy into heat but if the blood is caused to flow suddenly into a wider tube the decrease in velocity must cause a rise of pressure. This sounds paradoxical because the liquid is now flowing from a lower to a higher pressure. It is by the conversion of the kinetic energy into pressure, as for instance in the Pitot tube, which renders this possible. The filling of the ventricles by the auricles is possibly due to the kinetic energy of blood set in motion by the contraction of the auricles more than to a pressure produced in the auricles.

**Systolic and Diastolic Pressures.** With each beat of the heart the pressure in the arteries varies. For example if an artery is cut open and the blood allowed to squirt on to a travelling surface the variations in pressure will cause the trajectory to vary with the production of a haemautogram.

In the records obtained by the various instruments described the variations in pressure cause oscillations. With each variation in pressure there will also be a variation in velocity. One way of showing the variation in pressure is to observe the pulsation of the blood-vessels. A shadow of the vessels in the neck projected on a photographic surface will show the dilation due to increased pressure.

The arteries are elastic tubes, therefore they expand when the pressure in them increases, but apart from this increase in cross section there are other factors to be considered. The shape of an elastic tube is not always circular. The weight of the tube causes it to collapse so that the outline is more elliptical than circular; the higher the pressure inside, the nearer the tube approaches a circular outline. The elliptical outline can be exaggerated by

applying external pressure to the tube and this is what is done when the pulse is felt or recorded.

A length of artery is selected where it is supported by a solid structure, such as a bone, and the button of a recording instrument is pressed on the surface of the skin over the artery. As the pressure in the artery varies the wall will be pressed out or in and the greatest movement of the recorder will be when the pressure outside is between the extremes of pressure inside. The movements of the button are recorded either by using a tambour system or by a series of levers, but the same instrumental difficulties occur as in all mechanical systems of recording. Magnification by reflection of light is the most accurate, but it requires more complicated apparatus such as a source of light, lenses and camera with moving sensitized surface.



FIG. 57.—Haemautogram (Landois and Stirling).

Record obtained by allowing blood to squirt from an artery on a moving surface. The variation in pressure during the pulse beat is shown by the height of the tracing.

rise of pressure in the vessel. The wave of pressure travels down the vessels and becomes somewhat altered from that recorded in



FIG. 58.—Direct Pulsation Record of Shadow of Neck.

The expansion of the carotid artery with each pulse beat is shown without any distortion due to levers. Time marking in  $\frac{1}{5}$  secs. Contrast with Fig. 58. (Kindly lent by Dr. John Parkinson See Heart, Vol. VI.)

the aorta. The rise of pressure is flattened out, but owing to the inertia of most recorders the onset of the record is delayed. When

the recording system is in motion it is projected beyond the true curve, showing a spike at the top of the curve. The plateau shown in the aorta is rounded down so that in the smaller arteries the fall of pressure is a slow decline until the next pulse wave arrives. On the downward wave is a marked secondary wave preceded by a small depression; this is the dicrotic notch and the dicrotic wave.

The *dicrotic notch* indicates the effect of the closure of the semi-lunar valves on the pressure wave. The proof for this is that if the distance is measured between the commencement of the pulse wave and the dicrotic notch it will be found that this time interval is uniform and equal to the duration of the contraction of the ventricle. The mechanical factors responsible for the dicrotic notch and dicrotic wave are as follows. When the contraction of the ventricle ceases blood is no longer forced into the aorta. The blood in the aorta is however moving forward with a kinetic energy which can be measured by Pitot's tube. When the blood ceases to flow from the ventricle the kinetic energy carries the blood away from the aortic valves so that there is a fall of pressure at that point. This is comparable to the water hammer effect often noticed in a water pipe when the flow is suddenly checked.

A further consideration is that when the aortic valves are open they lie parallel to the walls of the aorta. When they close they move away from the walls, thus causing a change of volume. This space must be filled with blood which flows from other parts of the aorta. The onward flow of blood is retarded by the fall in pressure: blood flows back against the valves and a reflected wave of pressure follows the dicrotic notch forming the dicrotic wave. Thus there is a slight fall of pressure which produces the dicrotic notch after which the pressure rises again to produce the dicrotic wave. Other waves may be seen on the descending limb of the tracing but these are usually instrumental vibrations. Sometimes the upstroke is interrupted, making a step on the record. This is called an anacrotic pulse and is usually due to an obstruction to the outflow of blood from the heart.

*The Pulse Pressure.* The changes in pressure during the pulse give what is termed the pulse pressure. The highest pressure is that produced when the ventricle has just finished emptying into the aorta, i.e. when the artery is distended by the largest volume of blood: this is called the systolic pressure. During diastole of the heart the blood flows out of the arteries and the pressure falls until the next heart beat occurs. The lowest pressure just before the next pulse is called the diastolic pressure. As the pulse pressure is the difference between the systolic and diastolic pressures the systolic pressure is the diastolic pressure + the pulse pressure.

The systolic pressure is measured by the obliteration of the pulse as described before (p. 75). The diastolic pressure is measured by decreasing the pressure in the armlet.

If the pressure in an armlet is sufficiently high all the blood-vessels in the part surrounded by it will be squeezed empty and they will remain empty at all stages of the pulse beat. If the pressure in the armlet is less than systolic some blood will be forced into the empty vessels when the pressure somewhat rises above that in the armlet. This will cause an enlargement in the arm with consequent compression of the elastic bag between the arm and the inextensible bandage. If the pressure in the armlet is so low that the vessels are full even during diastole the expansion of the arm will be limited

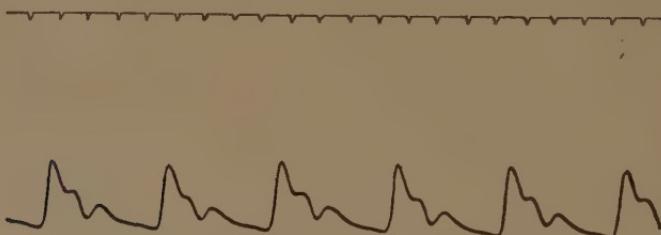


FIG. 59.—Record of Normal Radial Pulse.

Contrast the shape of the tracing with that shown in Fig. 58 where no levers are employed. Time marking in  $\frac{1}{2}$  secs. (Kindly lent by Dr. John Parkinson.)

to dilation of the vessel wall. It is clear that the maximum variation in volume of the arm will correspond to the condition in which the artery is empty between the beats and dilates fully when the pulse beat raises the pressure in the arteries. Therefore to obtain the *maximum oscillation* the pressure in the armlet must be at least as high as the lowest in the artery just before the next pulse wave arrives at the armlet. If the pressure is much above the diastolic pressure the artery cannot completely expand during the pulse and the variation in size of the arm will be less. Only that part of the rise in pressure which is above the pressure in the armlet will cause expansion of the arm.

This method of maximum oscillation is used as an indication of the diastolic pressure. Although oscillations occur in the mercury manometer these are greatly damped by the inertia of the mercury and the compressibility of the air in the conducting system. A device used in the Department of Physiology of The London Hospital for indicating the maximum oscillation is shown in Fig. 60.

The pressure recorder has a larger air space than usual. Between the pressure recorder and the armlet of the usual form of sphygmomanometer is introduced a U-tube containing water. As shown in the diagram there is a short circuit so that on pumping air into

the system the pressure rises in both armlet and manometer without affecting the water in the U-tube. On ceasing pumping the pressure can be read by the manometer. Now if the short circuit tube, C, is pinched, any variation in pressure in the armlet due to expansion of the arm will cause oscillation of the water in the U-tube. A large air space at the manometer increases the sensitiveness as it minimizes any variable compression of air on that side of the U-tube. The amount of oscillation is noted and the observation repeated at several different pressures. The lowest pressure at which the maximum oscillation occurs is thus determined.

A similar instrument is that of Pachon shown at B in Fig. 60. Two anæroid barometers are used, one inside the other. The outer one shows the pressure in the whole system. By closing the com-

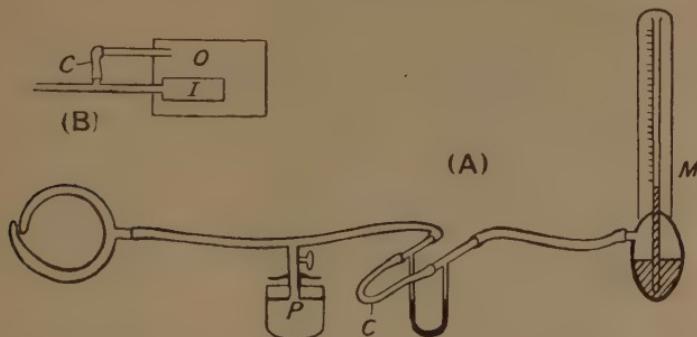


FIG. 60.—Diagram of Apparatus for Measuring Blood Pressure.

(A) Armlet with pump P and manometer M. At C is shown the rubber tube closure of which shows the oscillation in the U-tube due to expansion of the arm during systole. The pressure is noted in the manometer when the oscillation in the U-tube is maximum.

(B) Pachon's manometer. I = inner anæroid which shows oscillations when C is closed. O = outer anæroid which shows pressure in the system.

municating tube, C, the variations in pressure between O and I will cause oscillations of the indicator for the inner sensitive anæroid. The principle of these two is the same.

It is not generally accepted that the maximum oscillation shows the diastolic pressure. Another method is used to determine the diastolic pressure. If one listens with a stethoscope over an artery peripheral to the armlet one can recognize several different conditions. When the arteries are compressed so that they do not expand with systolic pressure no sound is heard. As the pressure in the armlet is decreased blood squeezes through at the height of the systolic pressure. This causes a tapping noise. As the pressure is allowed to fall slowly the sound gradually increases to a maximum and then fairly rapidly fades away (Korotkoff). The sudden change from a loud to a soft noise is said to be another method by which the diastolic pressure can be determined.

### Rate of Pulse Wave

The pulse does not appear synchronously in the whole arterial system. This can be demonstrated by measuring the time interval between records of the pulse made on arteries at different distances from the heart. If the recording systems are similar their inertias will be equal and the distances between the commencements of the records will show the time required to travel along the various lengths of artery. These differences are shown in Fig. 61.

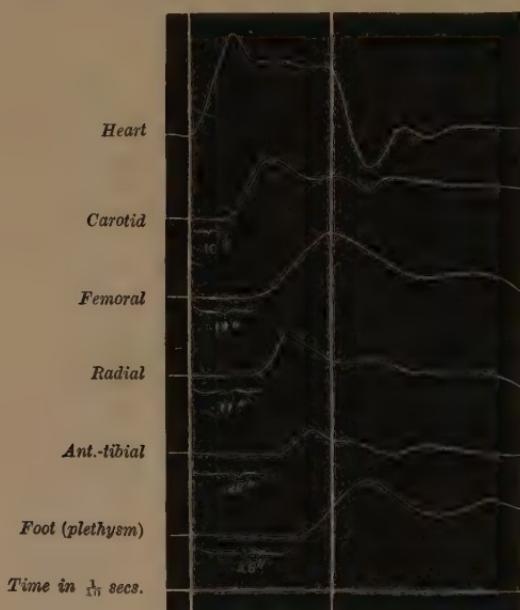


FIG. 61.—The Pulse Wave in the Arterial System (Waller).

The delay in the rise of the record shows the time required for the pulse wave to travel from the heart to the vessel from which the record is made. The shape of the curve varies in different arteries. Note that the pressure falls suddenly in the heart but only gradually in the arteries.

pressed in the following formula :

$$\text{Velocity of pulse} = k \sqrt{\frac{gea}{\Delta d}}$$

in which  $g$  = acceleration due to gravity,  $e$  = the coefficient of elasticity,  $a$  = the thickness of the vessel wall,  $d$  = diameter of the tube and  $\Delta$  = specific gravity of the fluid.

The constants  $k$ ,  $g$  and  $\Delta$  do not vary in the blood-vessels, but  $a$  and  $d$  will vary not only in different vessels but in the same vessel with differences in pressure.  $e$  will vary with the distension of the

The pulse is due to the distension of the arterial wall by blood. The extra pressure due to the distension forces the surplus blood into the next segment of the artery: this wave of pressure travels more rapidly than the blood. Its velocity is about ten metres per second in an adult man with normal blood pressure. The average velocity of the blood in the aorta is about 500 mm. per second, i.e. about one-twentieth of the rate of the pulse wave.

The velocity of the pulse wave depends upon a number of factors which are ex-

vessel wall—that is with the blood pressure, possibly with the state of the involuntary muscle in the vessel wall or with pathological changes in the wall.

*Venous blood pressure* in man has been measured by finding the pressure necessary to obliterate superficial veins. A glass plate rests on a rubber bag which has had a circular hole punched through both layers of the bag. The two sides of the bag adhere to the skin and glass plate respectively owing to the bag being smeared with vaseline. Air is pumped into the space between the glass plate and the skin and the pressure observed when the veins are emptied of blood (von Recklinghausen).

*Capillary blood pressure* has been measured by Roy and Graham Brown (1878) by a somewhat similar method. A thin membrane, such as the mesentery, is spread over a glass slide. Above the slide is a glass cell the bottom of which is formed by a thin translucent membrane. Pressure in the bag causes it to compress the peritoneum against the glass slide. This is observed under the microscope and the pressure noted when the circulation is stopped in the capillaries.

The pressure required to blanch the skin can be measured by a glass plate with weights supported on it. The weight divided by the area of the plate gives the pressure per sq. mm. This measurement includes the resistance of the skin in addition to the capillary pressure.

Near the heart there are variations in volume in the large veins. These may be recorded by placing an open metal receiver over the junction of the internal jugular and subclavian veins, i.e. over the space between the two heads of origin of the sterno-mastoid muscle. This receiver is connected by a rubber tubing to a recording tambour. When the auricle is contracting blood cannot pass from the veins into the right auricle, and as the flow continues in the tributary veins the volume in the large venous reservoir increases and the tambour records a rise ("a" wave). When the auricle relaxes there is a decrease in volume as the blood drains into the relaxed auricle. The auricle fills and as the ventricle contracts a second wave is recorded by the tambour ("c" wave). The "c" wave may be due partly to pulsation from the adjacent carotid artery and partly to the bulging of the auriculo-ventricular valves.

Towards the end of ventricular systole a third ("v") wave is recorded. This wave is probably due to continued flow from the veins so that the volume increases when the auricle has become filled. With the relaxation of the ventricle blood flows into it from the auricle which causes a final decrease in volume of the venous reservoir shown in Fig. 62 by the descent of the "v" wave.

The pulse is not usually felt in other veins, and if these are cut

the blood flows out steadily instead of in spurts ; the intermittent flow therefore in the arteries is converted into a constant flow. This is accomplished by the elasticity of the arteries. When the heart empties into the aorta the volume of blood in the latter is increased and the pressure rises. The increased volume causes a distension of the vessel wall and this distension maintains an increased pressure until the extra blood has flowed out of the arterial system. The maintained pressure forces blood onwards between the heart beats so that the flow from the arterioles is slightly varying

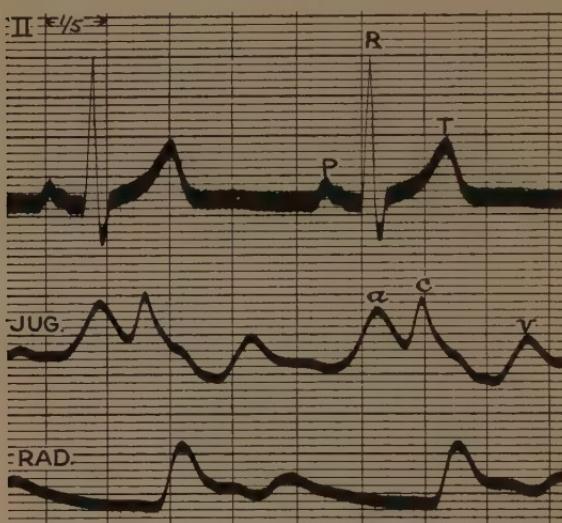


FIG. 62.—Simultaneous Record of Electrocardiogram, Jugular Pulse and Radial Pulse in a Normal Subject.

Jugular and radial pulses are recorded by tubes of the same length so that their time records are comparable, but they are delayed relatively to the electrocardiogram. The *a* wave of the jugular pulse corresponds to the contraction of the auricle. The *c* wave corresponds to the commencement of the ventricular systole, and the fall of the *v* wave marks the end of ventricular systole. The radial pulse is later in the record because of the time required for the pulse wave to reach the wrist. Time marking in  $\frac{1}{5}$  secs. (Kindly lent by Dr. John Parkinson.)

quire an exact measurement of the area of the cross section of the artery. It is not easy to measure the area of cross section because the artery is distended with blood and measurement must be made of the internal area of the artery.

The volume of blood is related to the velocity by multiplying the average velocity by the area. Volume = velocity  $\times$  area of cross section,

$$\text{or velocity} = \frac{\text{volume}}{\text{cross section}}.$$

in rate and not intermittent. Any slight variation of rate of flow is absorbed in the large lake of capillaries.

The velocity of the flow of blood varies in different arteries. The velocity is measured as the length of a column of blood passing through a cross-section of the artery per sec. All attempts to measure this velocity, as also all attempts to measure the volume of blood passing through an artery, re-

The velocity of flow can be measured by the instrument described in connection with the pressure due to onward movement of the blood (p. 75). Several instruments have been designed to measure the velocity of flow. In all of these the velocity is measured in the instrument and this must be corrected by the ratio of the cross section of the artery to that of the instrument so as to give the velocity in the artery. Chauveau's hæmodromograph is a vane fitting in a tube. The onward flow of liquid presses the vane to one side against an elastic pressure and the extent of deflection measures the velocity of the flow.

In all records of the velocity of blood flow it is clearly seen that the velocity of the flow varies with the pulse wave. Although the pulse wave travels more quickly than the blood contained in the vessel, changes in velocity occur corresponding to the changes in pressure due to the heart beat.

Having found the velocity of the flow in the instrument the velocity of the flow in the artery is given by the ratio

$$\frac{\text{Velocity of flow in instrument} \times \text{cross-section of artery}}{\text{Cross-section of instrument}}$$

The volume of blood flowing through an artery can be measured by allowing the blood to flow into a measuring vessel, but this method is not suitable for observations lasting a long period of time.

A simple method for measuring blood flow is to tie a measuring pipette into a side branch of a blood-vessel. By closing off the main vessel and leaving the branch to the pipette open the time required to fill a known volume can be measured with a stop watch. The blood may be taken for analysis or if the main vessel is opened the blood may be forced back into the circulation and the side branch closed until the next observation is to be made.

A slight modification of this is to use a U-tube and to measure the time required for the blood flowing through it to fill a known volume.

*Ludwig's Stromuhr.*—The further modification of this is to use Ludwig's "Stromuhr." This consists of two glass bulbs united at the top and mounted on a rotating plate so that it can be rotated on its vertical axis through 180°. Below this plate is a fixed plate with two openings corresponding to the openings of the bulbs. The use of this instrument is seen by consulting Fig. 63. Vessel A is filled with oil and vessel B with Ringer solution. Blood flows into A forcing oil to B and Ringer into the circulation. When all the oil is forced out of A (x c.c.) the instrument is turned through 180° so that blood now flows into B, driving the oil back to A and the blood out of A in the direction of the arrow into the circulation. The number of turns,  $y$ , of the instrument in a given time are noted.

Then  $x \times y =$  no. of c.c. in a given time. From this volume and the area of the artery the average velocity of the blood can be calculated. The velocity calculated from measurements of the volume of blood passing through in a given time does not give any indication of the variations in velocity which may have taken place during that time interval. The top of the instrument is closed by a clamp at C.

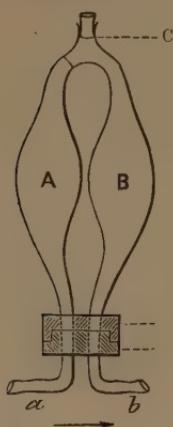


FIG. 63.—Ludwig's  
Stommuhr (from  
*Waller's Human  
Physiology*, Long-  
mans, Green &  
Co.)

Velocity of flow varies in different parts of the cross section of the same vessel. This is due to the fact that friction occurs between the vessel wall and the various layers of liquid in the tube. For instance the liquid in actual contact with the wall does not move whilst the most central part moves most rapidly. Owing to the fact that blood corpuscles are mainly confined to the "axial" stream they travel more rapidly than the plasma near the vessel walls; hence calculations of the volume of blood passing through a region based on oxygen transport are greater than if the calculation is made on the basis of the slower moving plasma.

Some results obtained by the methods described above are given in the following Table.

TABLE IV  
VELOCITY OF BLOOD IN DIFFERENT ARTERIES.

| <i>Blood-vessel.</i>              | <i>Velocity in mm.<br/>per second.</i> |
|-----------------------------------|--|
| Carotid artery of horse . . . . . | 300                                    |
| Carotid artery of dog . . . . .   | 520-150 <sup>1</sup>                   |
| Jugular vein . . . . .            | 147                                    |
| Femoral vein . . . . .            | 162                                    |
| Renal vein . . . . .              | 63                                     |
| Mesenteric vein . . . . .         | 85                                     |
| Capillaries . . . . .             | 0.5-0.9                                |

<sup>1</sup> This shows the variation that may occur during the heart beat.

**Time Necessary for Complete Circulation.** The time necessary for an object to pass round the circulation is an arbitrary measurement. Various substances have been injected into one jugular vein and detected at the other jugular. The substance will be detected as soon as it has completed the circulation by the shortest possible route in the axial stream. Ferrocyanide and methylene blue have been used as test substances, and even a

strong solution of sodium chloride which can be detected by a change in electrical conductivity in the opposite vein.

In a large series of animals it has been found that the circulation-time corresponds to about 28 heart beats. Therefore the actual time varies inversely with the rate of the heart beat as shown in the cases of : Horse 28.8, Dog 16.32 and Rabbit 7.46 seconds. In Man the circulation time would correspond to 23 seconds. Of this time at least 1 second will be spent in the systemic capillaries.

*Heart-Lung Preparation.* Artificial schemata may be used to demonstrate the factors involved in the circulation, but to study the action of the heart the heart-lung preparation is very useful.

The pulmonary circulation is maintained and the blood aerated by artificial ventilation of the lungs. The systemic circulation is represented by the apparatus shown in Fig. 64. The arterial pressure is measured by a manometer, M, and the elasticity of the blood-vessels is represented by an air cushion, B. The peripheral resistance is maintained by a thin-walled rubber tube which can be compressed from outside. The outflow is recorded by the automatic syphon, S, of which the volume emptied is known and each emptying is recorded by the tambour, D.

The inflow of blood into the heart is regulated by the height of the venous reservoir. Thus one can study the effect of inflow of blood, peripheral resistance, etc., on the work of the heart.

**Work of the Heart.** The work done by a pump consists of two parts, namely the work done in raising the pressure of a given

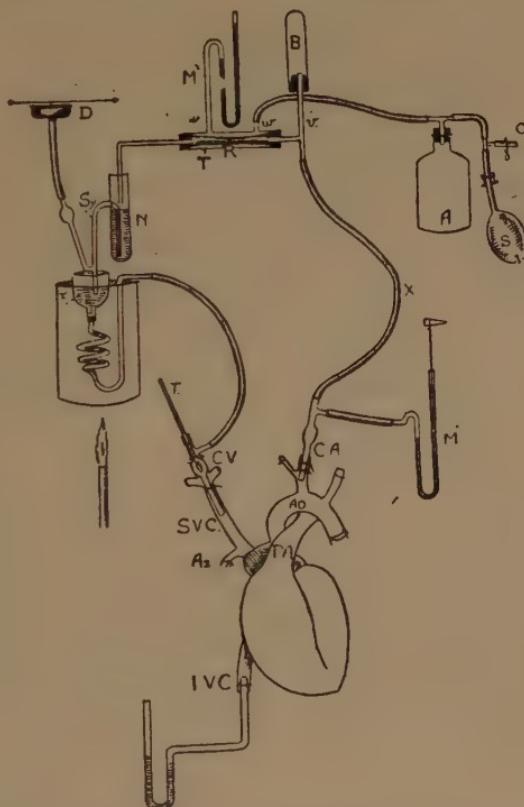


FIG. 64.—Diagram of Apparatus used in the Heart-Lung Preparation (Knowlton and Starling).

bulk of liquid and the work done in imparting kinetic energy to that liquid. If 60 c.c. of blood are sent out of each ventricle and the pressures in the aorta and pulmonary artery are 150 and 60 mm. of mercury respectively, and the velocity in each vessel is about 50 cm. per second we can estimate the work as follows :

$$\text{Work in grammetres} = \text{volume} \times \text{pressure in metres of water} + (\text{volume} \times \text{specific gravity} \times \text{velocity}^2) \div 2 \times 9.8.$$

$$\text{Left ventricle}, 60(0.15 \times 13.6) + [60 \times 1.06 \times (0.5)^2] \div 2 \times 9.8 = 112.4 + 0.8 = 113.2$$

$$\text{Right ventricle}, 60(0.06 \times 13.6) + [60 \times 1.06 \times (0.5)^2] \div 2 \times 9.8 = 49.0 + 0.8 = 49.8$$

Total work for both ventricles in grammetres = 163.0. 13.6 is the conversion factor for expressing the pressure of mercury in grams, 1.06 is the specific gravity of blood, and 9.8 is the conversion factor for gravity.

Such a calculation shows a very low value for the work done in imparting movement to the blood. It must be remembered, however, that the duration of the systole is only about 0.35 of a second, and even if we assume that the velocity is uniform throughout that period, the velocity of blood passing through the arterial orifices will be—

$$(\text{volume of output} \div \text{area of opening}) \div 0.3.$$

The formula worked out by Evans for both sides of the heart is  
 $\text{Work} = 7 \left( \frac{QR}{6} + \frac{MV^2}{g} \right)$ , where Q = volume of output, R = pressure in grams per sq. cm.

Table V shows some of the calculated results from which we see that the work done in imparting movement to the blood increases at a rapid rate as the velocity of emptying increases.

TABLE V  
 WORK DONE BY DOG'S HEART WITH AORTIC CANNULA OF 5 MM.  
 DIAMETER (EVANS).

| Output in litres per hour. | Mean Velocity in metres per sec. | $\frac{7eV^2}{g}$ per hour (both ventricles). |
|----------------------------|----------------------------------|---|
| 3                          | 0.042                            | 0.0038  |
| 12                         | 0.169                            | 0.253   |
| 36                         | 0.51                             | 6.72  |
| 48                         | 0.67                             | 15.4  |
| 60                         | 0.845                            | 30.7  |
| 72                         | 1.02                             | 53.7  |
| 84                         | 1.18                             | 84.2  |
| 96                         | 1.35                             | 125.0   |
| 108                        | 1.52                             | 179.0   |
| 120                        | 1.69                             | 245.0   |

*Viscosity.* One of the factors in the circulation is the viscosity of the circulating medium. The internal friction depends upon the nature of the fluid and the presence of suspended particles in it.

The coefficient of viscosity is usually measured by comparing the outflow of the liquid with the outflow of water under the same conditions of outflow as to pressure, length and diameter of tube and temperature. The simplest form of instrument is a pipette with a length of narrow capillary tube. The time required for a known volume of water to flow through the tube is compared with the time required for the fluid under investigation to flow through. If the rate of flow is not too rapid the relative viscosity is proportional to the time, but a correction must be introduced for the specific gravities of the solutions. The greater the specific gravity of the solution the greater the hydrostatic pressure ; therefore the greater the specific gravity, the shorter the time taken.

A known volume of distilled water flows out of the tube in 50 seconds. The same volume of blood, specific gravity 1.06, flows out in 210 seconds. The viscosity of the blood compared to water is

$$\frac{210}{50} \times \frac{1.06}{1.00} = 4.45.$$

It would require 4.45 times as much pressure to force blood through at the same rate as the water.

Suspended particles do not seriously affect the viscosity until they occupy about two-thirds of the total volume. Then the friction of one particle against another adds to the total resistance.

From Poiseuille's formula we see that the rate of flow in the various parts of the circulation is proportional to the difference in pressure of the portion being considered, the length of the vessels and the fourth power of the radius, the viscosity being taken as uniform throughout the circulation.<sup>1</sup> One very important factor is indicated by the fourth power of the radius in Poiseuille's formula, namely that the size of the vessel has a marked influence on the circulation. A contraction of circular muscle in the vessel wall will decrease the circumference in proportion to the extent of contraction. That is equivalent to saying that the radius is decreased in proportion to the extent of contraction of the muscle. A contraction of muscle to two-thirds of its length will cause a decrease in circula-

tion to the extent of  $\left(\frac{2}{3}\right)^4 = \frac{16}{81}$  or approximately  $\frac{1}{5}$ . Therefore to maintain the same rate of flow the difference in pressure would have to be increased five times.

<sup>1</sup> The viscosity may vary in different areas depending on alterations in the blood during its passage through these portions.

With each heart beat the pressure rises, and thus the flow is accelerated in the arterial circulation after each heart beat.

If the circulation of the blood is to be maintained the same amount of blood must pass through each section of the circulation (namely arteries, capillaries and veins) in a given time, otherwise the blood would accumulate in one part and the others would be deprived of blood. Variations in the circulation may occur as the result of alterations in the heart beat or the degree of contraction of the muscle walls, but these are more relative than absolute. Thus we see that the rate of flow is inversely proportional to the cross section of the part of the circulation being considered. All these points are illustrated in Fig. 65 which represents variations in pressure,

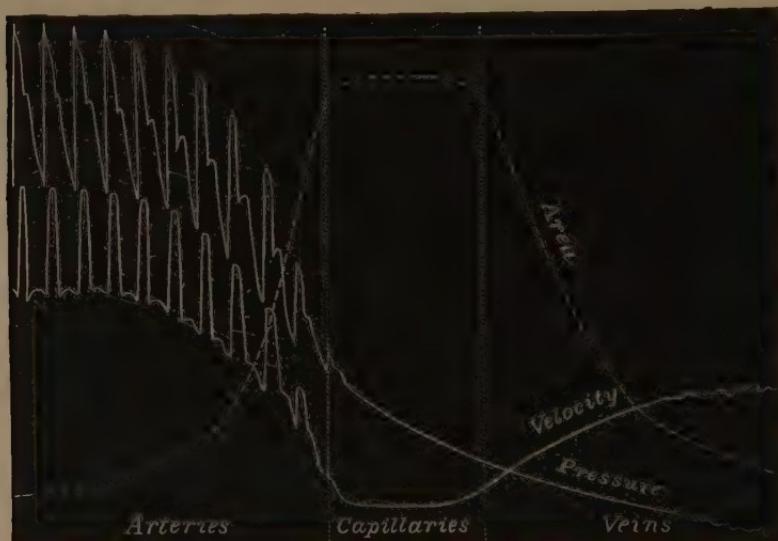


FIG. 65.—Diagram showing the Relations between Pressure, Velocity and Total Area in Arteries, Capillaries and Veins (Frédéricq).

rate of flow and cross section of the various portions of the circulation.

We see that in the large arteries the flow is free and the fall of pressure is slight. With decrease in size of the arteries the resistance increases as the fourth power. Although the number of vessels is greater the increase in area is not proportional to the increase in resistance, and thus the net result is a greater difference of blood pressure in the arterioles.

The capillaries are like a network and the rate of flow in them is slow. Owing to the great total sectional area of the capillary region the slow rate of flow is sufficient to pass blood through in sufficient amount without much difference in pressure. The veins having a

greater cross section than the corresponding arteries, the same amount of blood can pass through in the same time as through the arteries, but with less difference in pressure and with less velocity of flow. In addition near the heart variation in venous pressure due to the intermittent filling of the heart causes variations in flow (see Fig. 62).

In the preceding discussion it has been assumed that Poiseuille's formula represents the conditions in the blood-vessels. If turbulent flow occurred the resistance to the flow would increase. Such turbulent flow may occur where the blood is passing through narrowed parts, such as the openings from one part of the heart to another. Turbulent flow, however, is probably the exception as most observers have described the flow in blood-vessels as consisting of an axial core of corpuscles and an outer margin of plasma. This appearance shows that in the blood-vessels observed the flow is regular and not turbulent. Therefore statements that the resistance increases at a greater rate than the increase in velocity have no experimental basis.

## CHAPTER VII

### MINUTE STRUCTURE OF THE BODY

The structure of the body is related to its activities. We have seen how the bones and muscles, the former as levers, the latter as sources of energy, are related to the mechanical activities of the body. The minute structure of the body is also related to the physiological activity of the various parts. In this concluding chapter on the mechanical activities of the body a brief outline of histology will be given so that the student may be enabled to understand the other references to structure.

**The Cell.** Microscopic examination of the body reveals the fact that it is built up of small structural units called cells and a

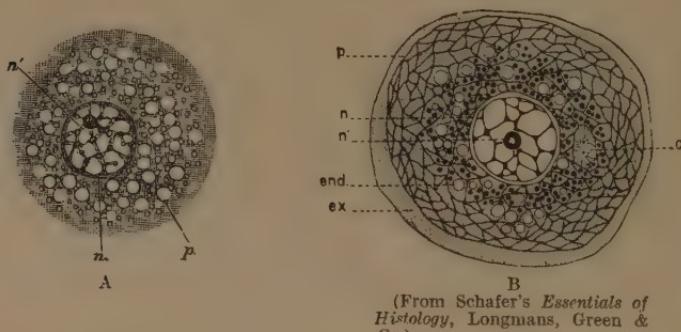


FIG. 66.—Diagrams of Cell-Structure.

A = diagram of a cell the protoplasm of which appears structureless but is occupied by vacuoles and granules.

B = diagram of a cell the protoplasm of which appears reticular or sponge-like. *p* = protoplasm (consisting in B of hyaloplasm and a network of spongioplasm); *n* = nucleus; *n'* = nucleolus; *c* = double centrosome; *end.* = endoplasm; *ex.* = exoplasm.

certain amount of material which links the cells together. According to the types of cells and the amount and nature of intercellular material we distinguish several different kinds of tissues. These tissues are built up into functional units or organs. The organs themselves are linked to form groups or systems, but the same organ may be related to several systems as all the activities of the body are ultimately linked together.

*Structure.* Although cells vary in formation we can describe a typical cell as consisting of a mass of living matter or protoplasm.

Contained in the protoplasm are certain structures. The chief of these structures is the nucleus which presents certain chemical differences from the rest of the cell. Another object which is frequently present is the centrosome. Various granules are stored in the cell, some of which may be recognized by specific chemical tests which will be given in the appropriate section.

The elementary tissues are of four kinds, namely : 1. Epithelia ; 2, Connective tissue ; 3, Muscular tissue ; 4, Nervous tissue.

### 1. EPITHELIA

An epithelium is a tissue composed mainly of cells and it always covers a surface. Between the cells is a small amount of cement material, and connecting protoplasmic bridges frequently unite the cells giving a prickle-like appearance to the tissue. An epithelium may be a simple epithelium composed of a single layer of cells or it may consist of several layers when it is called a compound epithelium.

#### Simple Epithelia.

The cells of a simple epithelium vary in height from flat cells to tall ones. Thus we differentiate between the following types of epithelium.

(1) *Pavement epithelium* consisting of a single layer of thin cells. These form the lining membranes of serous cavities, the vascular system and joint cavities.

(2) Somewhat thicker cells form *cubical epithelium*.

(3) Taller cells are called *columnar*, some of which are furnished with hair-like projections called *cilia*. Thus we distinguish between columnar epithelium and columnar ciliated epithelium.

A surface layer may be evaginated to form finger-like projections.

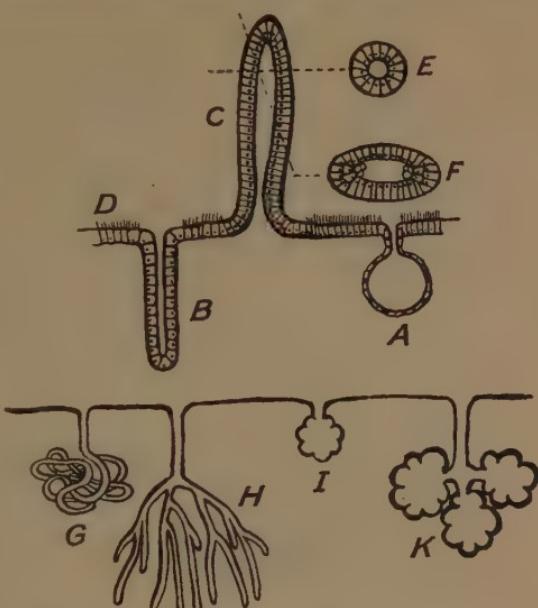


FIG. 67.—Types of Epithelial Cells and of Foldings of Epithelial Surfaces.

*A* = saccular gland with pavement cells. *B* = tubular gland with cubical cells. *C* = evagination of epithelium to form villus with columnar cells. *D* = surface layer of columnar ciliated cells. *E* = transverse section of villus. *F* = oblique section through villus corresponding to oblique dotted line. A similar appearance to *E* and *F* would be shown by transverse and oblique sections through a tubular gland. *G* = coiled tubular gland. *H* = compound tubular gland. *I* = saccular gland with alveoli *K* = compound saccular gland.

The villi of the small intestine are projections which may be cylindrical or approximate to a spheroid. A transverse section of such a projection would be circular in outline (E, Fig. 67), whilst an oblique section would be elliptical (F, Fig. 67).

When a surface layer is invaginated various types of glands are formed. A tubular gland consists of a cylindrical column of cells with a central lumen (C, Fig. 67). Such a gland may form a coiled tube as for example in the sweat glands (G, Fig. 67). Branched tubular glands are typical of many secreting glands (H, Fig. 67). A transverse section of a tubule will show a central hole surrounded

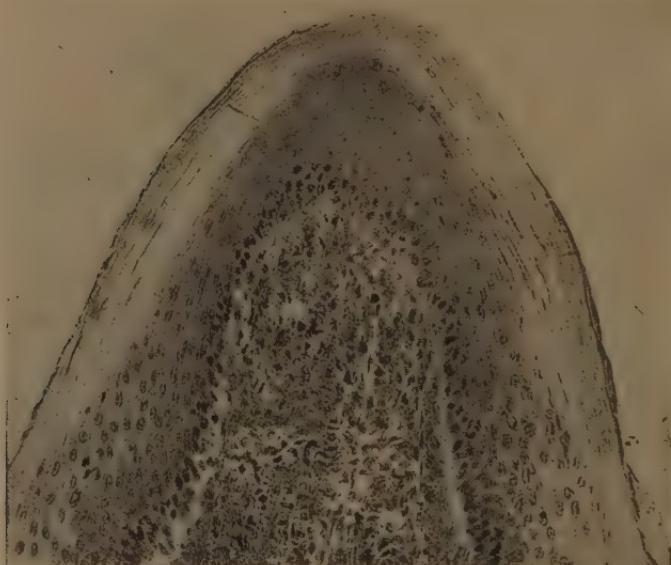


FIG. 68.—Photomicrograph of Stratified Epithelium on Conical Papilla of Tongue ( $\times 100$ ).

by a layer of cells but an oblique section will show an elliptical hole and an elliptical mass of cells (E and F, Fig. 67). Tubular glands are generally lined by columnar or cubical epithelial cells.

Saccular glands are also found corresponding to the spheroidal projections (A, Fig. 67). A section through such a gland will always show a relatively large lumen surrounded by cells. A multilobular saccular gland can be formed by alveoli opening into a central space (I, Fig. 67). A compound saccular gland is formed by branching ducts each of which may have a multilobulated sac opening into it (K, Fig. 67). The epithelium lining of a saccular gland is usually composed of either cubical or pavement cells.

**Compound Epithelia.** When a large number of layers of cells

are present we find that they are arranged so that the deeper layers are tall, the intermediate layers are more or less cubical, and the superficial layers are pavement. The whole forms what is called a *stratified epithelium* because the layers are arranged in strata. An intermediate condition in which three or four layers of cells are present is known as *transitional epithelium*. These are not arranged in definite layers and the cells are frequently irregular, for instance pyriform, in shape.

## 2. CONNECTIVE TISSUES

In these tissues the cells are fewer than in epithelia, and there is much intercellular material. The intercellular material varies according to the function of the tissue. Connective tissue when designed to hold structures together with a certain amount of movement, is formed of fibres running in various directions. The fibres are of two kinds, namely, wavy fibres running in bundles, and straight, single, branching fibres. The former are white fibres, and the latter are elastic fibres. They also differ in their reaction to acetic acid; white fibres swell and become transparent with acetic acid, whilst the elastic fibres remain unchanged. The cells are of various kinds. Some of the cells are wandering cells of variable shape



FIG. 70.—Photomicrograph of Areolar Connective Tissue ( $\times 100$ ).

Wavy bundles of unbranched white fibres and single, straight, branched elastic fibres are shown.

whilst others are fixed, generally fusiform or branched pointed cells. This form of tissue is *areolar connective tissue*.

Where the tissue is designed to withstand a pull in one direction



FIG. 69.—Photomicrograph of Transitional Epithelium from Bladder of Monkey ( $\times 100$ ).

the fibres all run in that direction. Just as a rope has fibres all running in one direction to withstand a pull, whilst a fishing net can be used to hold structures together with a certain amount of relative movement between the parts. So we find tissues with fibres all running in the same direction, and others again in which the fibres form a network. If the fibres are all white fibres the mass of fibres forms a *tendon*. The cells are placed in rows rather like a row of bricks. If the fibres are all elastic fibres they form *yellow elastic tissue*. In some other forms of connective tissue the intercellular material is solid. By the deposition of a firm gelatinous material between the cells *cartilage* is formed. The cells are con-

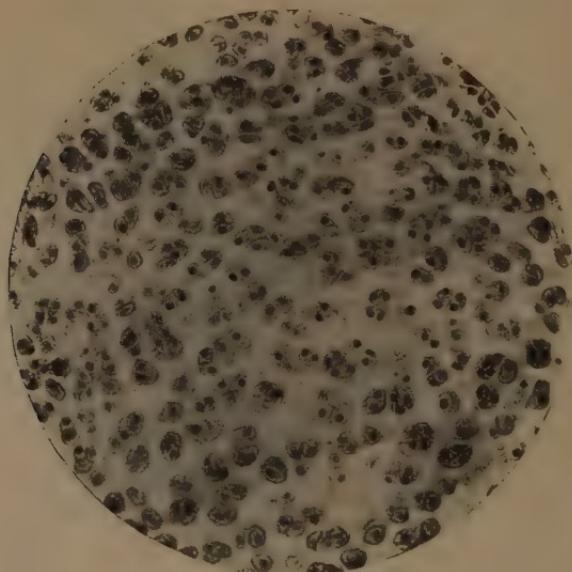


FIG. 71.—Photomicrograph of Hyaline Cartilage ( $\times 100$ ).

tained in special cavities forming round or oval capsules. When fibres are deposited in the homogeneous matrix it becomes either white fibro-cartilage or yellow elastic cartilage, according to whether the fibres are white or elastic. Cartilage is found where a firm elastic support is required such as in the ribs (costal cartilage) or covering the articular surface of bones (articular cartilage).

Deposition of calcium salts leads to calcification of tissue which is generally in the form of bone. In bone the cells lie in small spaces or lacunæ with fine canals running outwards, viz. canaliculæ. The cells are usually arranged in concentric circles round a central hole which contains a blood-vessel. This arrangement is known as an *haversian system*.



FIG. 72 A.



FIG. 72 B.

FIG. 72 A.—Diagram of Section through Haversian System in Bone showing Concentric Lacunæ and Radial Canaliculæ. B.—Photomicrograph of same ( $\times 100$ ).

The concentric rows of lacunæ with canaliculæ coming off from them are shown.

A very special form of tissue is that in which the intercellular material is liquid. This form has developed in multicellular animals as the result of the necessity for the transport of nutritive and waste materials. The cells are of various shapes and some of them possess the power of independent movement like an amœba, hence known as *amœboid movement*. These tissues form blood and lymph. They are described elsewhere (p. 224). They are usually regarded as connective tissues because the cells contained in them are developed in connective tissues such as bone marrow and lymphoid tissues.

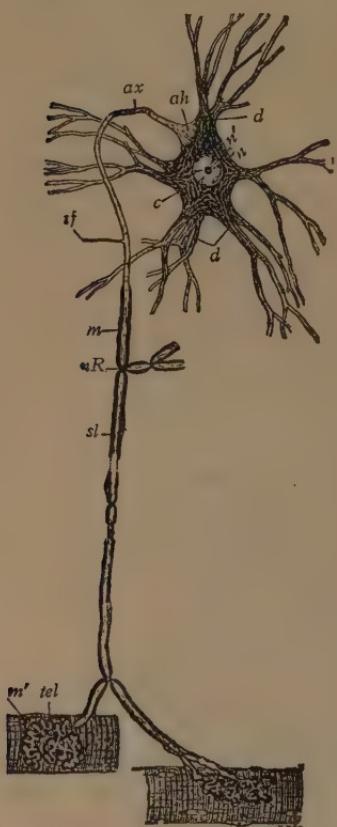


FIG. 73.—Primary Motor Neuron (diagrammatic).

*ah*, Implantation cone of axon; *ax*, axon; *c*, cytoplasm; *d*, dendrites; *m*, myelin sheath; *m'*, striated muscle; *n*, nucleus; *n'*, nucleolus; *nR*, node of Ranvier; *sf*, collateral; *sl*, neurilemma; *tel*, motor end-plate (Barker, Bailey).

striation in the cells and a central nucleus.

#### NERVOUS TISSUE

The function of nervous tissue is to correlate the activities of the various parts of the body. Its distinguishing feature is the presence of conducting processes or nerve fibres. The cell consists

and lymph. They are described elsewhere (p. 224). They are usually regarded as connective tissues because the cells contained in them are developed in connective tissues such as bone marrow and lymphoid tissues.

#### MUSCLE TISSUE

This, as described in Chapter II, consists of three varieties. Its function is to shorten, varying the elastic tension between its two extremities.

(a) **Striated Muscle.** This consists of cylinders about 4 cm. long with cross striations and many nuclei. It therefore represents a syncytium composed of many cells. The syncytium is surrounded by a limiting membrane known as sarcolemma.

(b) **Smooth muscle** consists of single fusiform cells each containing a nucleus. They are usually united in masses to form sheets of muscle.

(c) **Cardiac muscle.** The heart consists of a syncytium of branching cells. Although it is a syncytium because of the continuity of the protoplasm between neighbouring cells, yet there are definite cell outlines corresponding to a cell for each nucleus. There is a faint cross

of a cell body containing a nucleus and the processes projecting from the cell body. The whole is called a neuron. The cell body is variable in shape, consisting of spheres, spheroids, stellate bodies, pyramidal bodies, etc. Some of the processes are short, forming connections with neighbouring cells; these are called dendrons. There is usually one long process called an axone, which conducts to a more distant part. These processes are comparatively long as they may extend, for instance, from the lumbar region of the cord to the foot. These form the nerve fibres which are found in the nerve trunks. The nerve fibres are of two kinds: (a) *Non-myelinated Nerves* in which the axis cylinder or cell process is surrounded by a membrane called neurolemma. At intervals there are nuclei between the neurolemma and the axon. (b) *Myelinated Nerves*. These differ from the above in that each nucleus has surrounding it a mass of fat-like material. This fatty material forms a sheath for the axon called the myelin sheath. It extends for a certain distance and ends in close proximity to the fatty material of the

FIG. 74.—Non-  
Myelinated  
Nerve Fibres  
( $\times 400$ )

(From Schafer's  
*Essentials of Histology*. Longmans,  
Green & Co.).

The nuclei are  
seen at intervals.

Myelinated Nerve Fibres stained with Osmic Acid from a Young Animal. Diagrammatic from a sketch by J. E. Neale.

(From Quain's *Anatomy*, Longmans, Green & Co.)

*R, R* = nodes or constrictions of Ranvier with axis cylinder passing through. *a* = neurolemma, *c* = nucleus and protoplasm lying between the neurolemma and the myelin sheath.



FIG. 75. Portions of Two Myelinated Nerve Fibres stained with Osmic Acid from a Young Animal. Diagrammatic from a sketch by J. E. Neale.

next section. These interruptions leave a narrow interval called a node of Ranvier where the neurolemma and axon are the only elements in the nerve fibre. Each internode contains one nucleus and it may be regarded as a large fat cell surrounding the axon.

### Histological Methods

As the tissues described above form the materials from which the body is constituted, it is essential that the student should learn to recognize them so that from the tissues visible and the way in which they are arranged the actual organ which is present can be determined. This is most important for the student because unless he can recognize the tissues and the way in which they are arranged to form normal organs he will not be in a position to recognize abnormalities when he commences to study pathology.

A few words may be appropriate in reference to the way in which tissues may be studied. Large masses of material cannot be used as a rule. It is true that with strong surface illumination the surface layers may be observed, but for deeper portions the tissue must be divided into small thin pieces. In many cases fresh preparations may be made. Thus blood and soft tissues may be smeared on glass to form thin films. Other tissues, composed either of fibres which can be pulled apart, e.g. muscle, nerve, tendon or of layers which may be pulled apart and spread out flat, may be teased, i.e. torn up by needles. This may be aided by chemical (macerating) processes.

Finally thin sections may be cut by a sharp knife. This last method has been developed considerably by the construction of apparatus for the mechanical cutting of sections and by the process of rendering the tissue firm by freezing or by impregnating it with some firm but easily cut material such as paraffin or celloidin.

The process of impregnating the tissue becomes rather complicated as it is necessary to remove water from the tissue, and most substances that mix with water do not dissolve paraffin, hence it is necessary to pass the tissue through a series of liquids. First water is removed by alcohol; alcohol is next removed by some liquid that will also dissolve paraffin (such as xylol, cedar wood oil, etc.); the tissue is then soaked in molten paraffin. For further details as to this technical procedure the student should consult a book on practical Histology.

When sections have been cut they may be so thin and transparent that the structures are not clearly visible. Therefore methods are used to distinguish one part from another. Chemical precipitates may be produced by the interaction of some definite chemical substance. Silver and gold salts, etc. are used in this way. (See Table VI, p. 102.)

**Staining.** Like the process of dyeing staining is not easily explained, but it depends partly on chemical processes and partly on physical differences. A good analogy is to use pieces of cloth and compare their dyeing properties with the staining of tissues. If pieces of white cotton, wool and silk, are placed in a solution of congo red for a short time and then washed, it will be found that the cotton is the most deeply stained. Three other pieces, one each of the same materials placed in picric acid solution will show that the wool and silk are preferentially stained yellow. A third test with these materials is interesting. A mixture of congo red and picric acid is used, which has been neutralized, so that the congo red is in the red or alkaline condition. The materials placed in this and examined after washing will show some stained red (cotton) and some stained yellow (wool) whilst the silk may show an orange tint. This is analogous to staining a tissue by a solution containing two substantive stains.

Some stains will not colour the tissue unless a mordant is present. For instance alizarin will not dye cotton in the absence of a mordant such as a ferric, aluminium, copper, or other metallic salt of a weak acid. Similarly hæmatoxylin is always combined with a mordant such as alum or a ferric salt.

A slightly different method is to overstain the tissue and to remove the excess of stain by some solvent so that it is removed from some parts, and the other parts from which the stain is less rapidly removed remain coloured. This is more troublesome to perform, but it gives remarkably sharp definition of some structures.

Thus we see that the structure of the tissues may be demonstrated by precipitation of insoluble metallic substances, by staining with substantive dyes, by staining with a dye which requires a mordant either with it or applied previously, and by overstaining and differentiating with a suitable solvent.

### Structure of Organs

When we commence to study the structure of organs we must remember that sections show only one plane of the structure and that several sections should be made, if possible, in two or three planes at right angles to each other. Reconstructions are useful in that they enable one to understand the real structure of an organ.

Let us take as an example a simple tubular gland. If cut longitudinally it presents the appearance shown at A (Fig. 67). If cut transversely it appears as seen at E, whilst if cut diagonally we would see it like F. When there are a large mass of tubules together we cannot cut them all in the same direction, therefore outlines of various shapes will be seen as shown in Fig. 67.

TABLE VI

## METHODS OF STAINING HISTOLOGICAL PREPARATIONS

| <i>Stain.</i>                             | <i>Structure Demonstrated.</i>  |
|---|---|
| <b>1. Direct Chemical Reactions :</b>     |   |
| Silver nitrate . . . . .                  | Chlorides present in intercellular spaces.  |
| Gold chloride . . . . .                   | Stains purple by reducing agents,<br>usually demonstrating nerve endings.             |
| Osmic acid . . . . .                      | Stains black on reduction, e.g. by<br>unsaturated fats.                               |
| <b>2. Substantive Stains :</b>            |   |
| Eosin . . . . .                           | Cytoplasmic (non-nuclear) structures.   |
| Picric acid . . . . .                     | Cytoplasmic (non-nuclear) structures.   |
| Methylene blue . . . . .                  | Nuclei and certain granules.  |
| Orcin . . . . .                           | Elastic fibres.   |
| Acid fuchsin. . . . .                     | White fibres.   |
| <b>3. Stains requiring Mordants :</b>     |   |
| Hæmatoxylin . . . . .                     | Nuclear structures.   |
| <b>4. Stains for Specific Materials :</b> |   |
| Sudan III . . . . .                       | Fats.   |
| Scharlach R.. . . . .                     | Fats.   |
| Iodine . . . . .                          | Glycogen.   |
| Potassium ferro-cyanide.                  | Iron deposits.  |
| Hæmatoxylin . . . . .                     | As hæmatoxylin requires a mordant,<br>pure hæmatoxylin is used as a test<br>for iron. |

One of the consequences of the collection of cells into masses is that they must be supplied with nutriment and arrangements must be made for the removal of waste products. Diffusion is too slow for long distances, therefore a liquid is used in the form of blood and lymph. There are two different ways in which blood may come into relation with cells. (1) As the cells develop into definite structures such as glands the blood-vessels grow in amongst them in the form of capillaries. (2) On the other hand the cells may grow as columns into blood sinuses. The latter method of growth leads to the formation of narrow spaces filled with blood without a definite capillary wall. The spaces are somewhat irregular and are called sinusoids in contradistinction to true capillaries. Figs. 76 and 77 illustrate stages in the development of the chick's liver showing how the columns of liver cells grow into and fill the sinus-like space so that sinusoids are formed.

To appreciate the importance of blood-vessels to the tissues one must understand the relation of diffusion to the size of objects. Diffusion coefficients show the amount of substance which diffuses through a sq. cm. in a day, when there is unit difference of concentration at a distance one cm. apart. One of the factors that determines the rate of diffusion is the distance. If instead of measuring in cms. we use cellular dimensions, eg.  $10\ \mu = 0.010\text{mm}.$ , the rate of diffusion for the same difference of concentration would

be 1,000 times as great. Now the time taken for a substance to diffuse a given distance is the rate of diffusion divided by the dis-



FIG. 76.—Developing Liver of Chick.

(From Quain's *Anatomy*, Longmans, Green & Co.)

The illustration shows how the hepatic trabeculae encroach on the lumina of the sinus-like veins and break them up ultimately into the capillary-like channels called sinusoids (Minot).  
*hc* = hepatic trabeculae, *Si* = sinusoids.

tance. Therefore in order to convey a given amount of substance



FIG. 77.—Developing Liver of Chick.

(From Quain's *Anatomy*, Longmans, Green & Co.)

Later stage (11 days) than Fig. 76 to show narrowing of sinus-like spaces by further growth of the hepatic trabeculae (Minot).  
*hc* = hepatic trabeculae, *Si* = sinusoids.

for  $10 \mu$  would only occupy one-thousanth of the time that it would take to diffuse 1 cm. Thus for the same difference of concentration

the amount of substance entering the cell will be  $(1000)^2$  or  $10^6$  times as much as if the distance were 1,000 times as great. The blood by mass movement rapidly transports its various constituents and brings them close to the cells.

In order to show the relation of the cells of organs to the blood-vessels the method of injection is used.

The blood is washed out of the blood-vessels by a saline solution and the injection material is forced into the blood-vessels by gentle pressure. The injection material is such that it solidifies in the vessels, hence warm gelatin solution is the usual injection medium. The gelatin contains a non-diffusible dye which is not too transparent. Carmine which has been precipitated in a finely divided condition by means of acetic acid from ammoniacal solution gives an insoluble precipitate which produces an opaque mass, hence it shows up the blood spaces distinctly. Other pigments may be used in a similar way.

The individual organs will be considered in their appropriate place, but here we shall state the general manner in which organs are formed. For instance the skin consists of an inelastic layer of epithelium supported on areolar connective tissue. The connective tissue conveys the blood-vessel and allows the epithelium to slide over the deeper layers thus preventing injury, because a glancing blow is absorbed in a buffer-like manner by the yielding of the areolar tissue. It is also due to the areolar tissue that we can pinch the skin into folds.

Next let us consider a hollow organ such as the intestine. There is an epithelial layer supported on areolar tissue and external to the areolar tissue are muscle layers. The muscle layers are for the purpose of exerting a pressure on the contents. When the tissue is prepared for histological examination the muscle contracts, hence the inelastic epithelium is generally thrown into folds by the yielding of the areolar tissue. If it were not for the flexibility of areolar tissue the tube would not be distensible. If it were not for the sliding of the epithelium over the muscle by means of the areolar tissue either the organ could not collapse when empty or severe stretching pain would be caused when the organ was filled.

Both the skin and intestine contain other structures. First the surface epithelium grows downwards in tubes to form glands. Those in the intestine are tubular glands. In the skin there are two sorts, one tubular which has grown down further and forms a coiled mass (sweat glands), the other forming dilated alveoli or saccular glands (sebaceous glands).

Into the interior of the small intestine project finger-like processes. It is characteristic structures like these villi that enable one to distinguish the small intestine from the large. The large secreting

glands such as the salivary glands, pancreas and liver are formed by down growths from epithelial surfaces. As the gland becomes longer the more superficial part becomes differentiated as a duct whilst the deeper part branches to form a compound gland. When a section is cut through such a gland the tubules are cut at all sorts of angles so that some are cut transversely, others obliquely and portions again longitudinally.

The connective tissue and blood-vessels ramify between the



FIG. 78.—Photomicrograph of Lung ( $\times 100$ ).  
The pavement cells are seen dividing the air spaces into alveoli.

tubules. Great variations may occur in such glandular structures. For instance the lung is a saccular gland in which the sacs have been stretched to form large air sacs (infundibula) and the cubical epithelium has become flattened to form a pavement epithelium.

The relation of structure to function is well seen in the blood-vessels. These have typically three coats. An inner coat (intima) consists of pavement cells with a small amount of connective tissue and is supported on an elastic lamina. The middle coat (media) is

muscular with a certain amount of elastic and white fibrous tissue. The outer coat (adventitia) is composed of white fibrous and elastic tissues.

In the large arteries which are distended by a high pressure the elastic tissue is increased in amount. This enables them to exert a pressure on the contents between the heart beats, converting the intermittent output from the heart into a continuous flow.

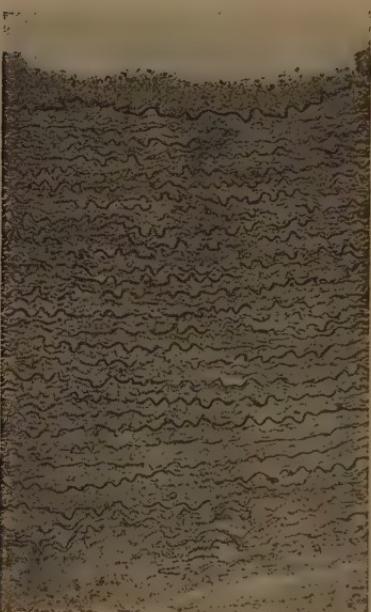


FIG. 79.—Photomicrograph of Large Artery ( $\times 88$ ).

Note layers of elastic tissue thrown into folds by the contraction of the muscle fibres during the fixation of the vessel.

the body by the voluntary muscles, the movements of the respiratory apparatus and the movements of the blood in the blood-vessels as the result of the pumping action of the heart.

**NOTE.**—For further information on the subjects dealt with in this part, the student should consult W. M. Feldman, *Biomathematics* (Griffin).

In the smaller arteries and heart where variation in size is more important the muscular layer is predominant.

In the veins the elastic tissue is largely replaced by white fibrous tissue but muscle is also present.

Owing to the large amount of connective tissue in their walls the veins are much more resistant to distension than are arteries.

The simple mechanical processes described in this part furnish a basis from which to discuss the physiological variations in the later parts of this book. Other branches of physics such as light and sound must also be dealt with, but they are more conveniently relegated to later chapters, such as those on vision and hearing. All that has been attempted here is a discussion of the mechanical factors concerned in such problems of animal mechanics as the movements of

## PART II

### CHEMICAL ASPECTS

Having gained some insight into the mechanical processes that occur in the body we must now study the means by which these mechanical processes are produced.

The accomplishment of work requires a supply of energy which must at least be as great as the amount of energy set free in the form of work. This is stated in the first law of Thermodynamics, namely that energy is neither created nor destroyed but merely converted from one form into another. As all forms of energy can be converted into heat it is customary in physiology to use the heat-unit in all calculations. The calorie (c) is the amount of heat required to raise the temperature of one gramme of water from 15° to 16° C. The large calorie (C) is one thousand times as great, namely the amount of heat required to warm one kilogramme of water from 15° to 16° C. In the conversion of kinetic energy into heat 426 kilogrammetres equal one large calorie.

The energy supply of animals is obtained by oxidation of the absorbed food materials. This oxidation is shown by the changes that take place in the air during respiration. The air is breathed in as atmospheric air and is breathed out as expired air which contains less oxygen, more carbon dioxide and more water vapour, and it is warmer than the inspired air. Compare these changes with those taking place in a furnace. The flue gases contain less oxygen and more carbon dioxide than the air that enters the furnace.

The chemical energy which becomes available during oxidation is contained in the food materials. Plants absorb carbon dioxide and under the influence of light in the presence of chlorophyll the carbon dioxide is reduced to substances capable of yielding energy on oxidation. This reduction of carbon dioxide is of fundamental importance as it forms the basis for the production of all energy-yielding food materials.

The chemical substances which form the medium of this energy transformation are considered in this part. We shall commence with a consideration of food materials, pass on to a study of the substances excreted and finally describe the processes by which the food is converted into the waste products.

## CHAPTER VIII

### FOODS

The first food which is consumed by the newly-born mammal is milk. This can be separated into a number of different fractions in much the same way as one can separate pure substances in organic chemistry. We shall describe the process of separation in order to show what classes of substances may be present in a food.

#### Milk

By careful addition of dilute acetic acid to diluted milk a curdy precipitate is formed which can be easily filtered off so that the milk is separated into a white precipitate and a transparent solution. Each of these can be examined further. This separation suggests

that there is something in milk of the nature of an insoluble organic acid which is precipitated by acetic acid.

The precipitate can be resuspended to form a white opaque suspension by the addition of alkali. By examination of this with the microscope it can be shown that the suspended particles are in the form of spheres. A similar appearance can be seen in milk showing that part of the whiteness of milk is due to reflection of light from these spheres. The presence of suspended material leads one to test the solubility of the suspended substance in other solvents. If the precipitate

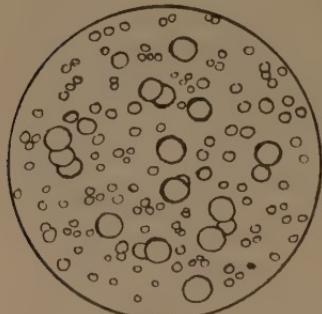


FIG. 80.—Drawing of a Drop of Milk under the Microscope ( $\times 300$ ).

The fat globules are seen as small spheres.

caused by the addition of acetic acid to milk be extracted with ether (or some other similar solvent), it can be separated into a portion soluble in ether and a portion insoluble in ether but soluble in alkalies. The former is left on evaporation of the solvent as a non-crystalline smeary substance which is best shown by the greasy stain left on evaporation of the solution on a clean glass slide. This property of forming a greasy stain on glass together with the solubility in organic solvents is characteristic of the group of substances known as fats.

The other substance which behaves like an organic acid insoluble in water but forming soluble salts belongs to the group of substances known as proteins. It is called caseinogen.

If now we return to the solution left after filtering off the caseinogen and fat we may separate another substance by carefully neutralizing and heating. A white precipitate is formed which can be filtered off and examined. It is another kind of protein known as lactalbumin. This property of forming an insoluble precipitate (coagulation) on heating is the distinguishing feature of certain kinds of proteins.

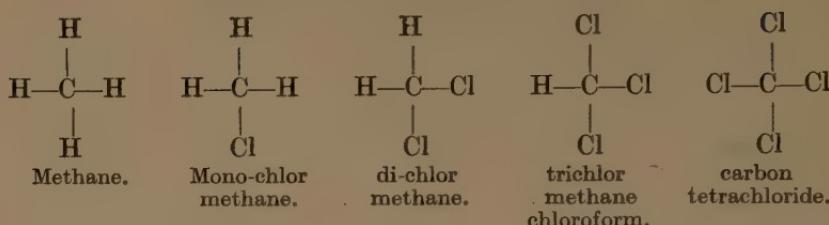
The solution left after removal of the lactalbumin still contains organic material as shown by the deposit of carbon formed when some of the solution is evaporated to dryness and heated in a flame. We can test for one organic substance by heating the solution after the addition of a cupric salt and alkali, when a dark red precipitate is formed due to the reduction of the cupric salt to cuprous oxide. The reduction of the copper is brought about by the oxidation of a sugar known as lactose or milk sugar. In addition to lactose the solution contains inorganic ions which can be tested for in the usual way. Amongst these we find sodium, calcium, chlorine and phosphate ions.

The four organic substances shown by the above process to be present in milk belong to three great classes of food materials, namely, *carbohydrates*, *fats* and *proteins*.

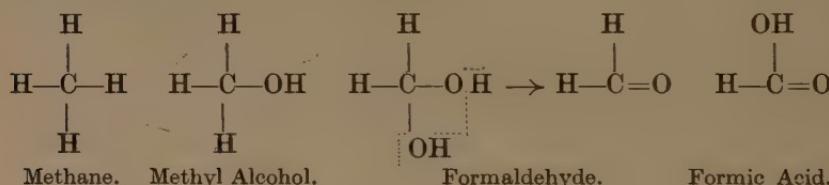
All these food substances can be shown to contain carbon by the simple expedient of heating them until they char leaving a black mass of carbon. If we oxidize them the carbon can be shown in the form of carbon dioxide as in the experiment on expired air (p. 234). The presence of hydrogen can be shown by the formation of water when some of the *dried* material is oxidized. It is not easy to show the presence of oxygen as there is no simple test for it. Two of the above groups, namely carbohydrates and fats, are composed of carbon, hydrogen and oxygen. But the third group, protein, contains nitrogen in addition.

The simplest way to approach the chemistry of the food substances is to remember that in general carbon is tetravalent, which means that it is capable of combining with four separate univalent atoms or some other distribution of four single valencies. If a single carbon atom is united with four hydrogen atoms or if a series of carbon atoms are united to each other and the remaining valencies united with hydrogen, the paraffin series of aliphatic compounds is formed.

Hydrogen atoms may be replaced by other elements or groups of elements. Thus starting with the simplest paraffin, methane, we can form a series of chlorides.



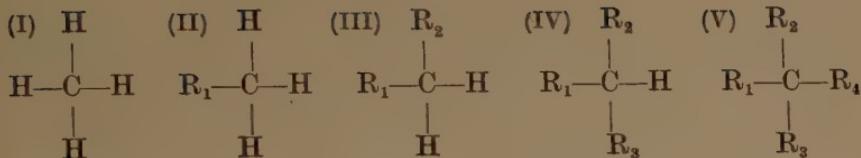
If we oxidize a paraffin we introduce an oxygen atom into it. As oxygen is divalent it may either replace two hydrogen atoms or be linked between carbon and hydrogen atoms. The latter is regarded as the first stage of oxidation. For instance methane on oxidation forms methyl alcohol. Further oxidation of methyl alcohol yields formaldehyde. The latter can be looked upon as the further oxidation of methyl alcohol so that two hydroxyl groups are formed which split off water, leaving one oxygen atom united to the carbon atom by two bonds.



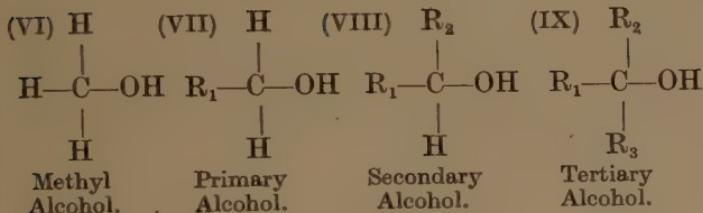
A further oxidation of formaldehyde gives rise to formic acid. This series of oxidations represents much of the chemistry of the carbohydrates and fats. It seems that usually whenever more than one hydroxyl group would be formed attached to the same carbon atom water is split off and an oxygen atom takes the place of two hydroxyl groups.

Now if we replace the hydrogen atoms by some other groups which for our purposes are generally a series of carbon atoms with similar properties to those that we have represented in methane we obtain many different substances. If we represent the substituting groups by R<sub>1</sub>, R<sub>2</sub>, etc., we see that by introducing a single group (R<sub>1</sub>) into methane we obtain a CH<sub>3</sub> group (Formula II), which is characteristic of the unoxidized end group of carbon atoms. If we introduce two groups (R<sub>1</sub> and R<sub>2</sub>) into methane we have left a CH<sub>2</sub> group (Formula III), which is characteristic of the unoxidized intermediate groups in a chain. Finally by introducing three groups (R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub>) a CH group is left which occurs at the junction point of a branching chain of carbon atoms (Formula IV).

A further possibility is the replacement of the four hydrogen atoms by four groups (Formula V).



Methane.

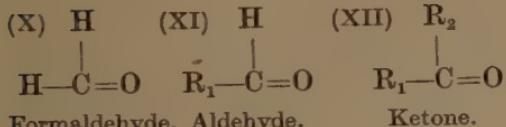


Methyl Alcohol.

Primary Alcohol.

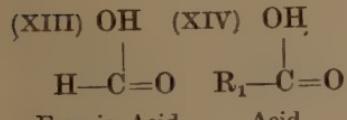
Secondary Alcohol.

Tertiary Alcohol.



Formaldehyde. Aldehyde.

Ketone.

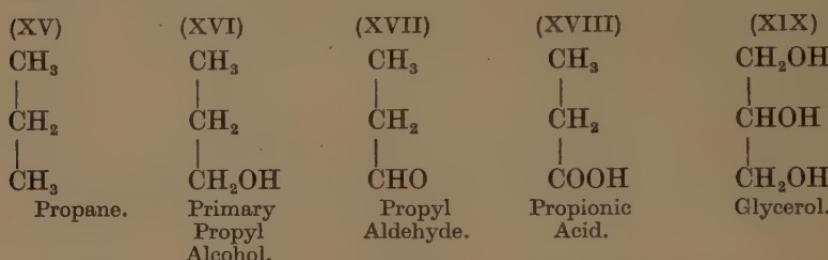


Formic Acid.

Acid.

The oxidation of these groups gives rise first of all to alcohols which are characterized by one hydroxyl group attached to the carbon atom. There are three varieties of alcohols depending on the number of hydrogen atoms left united to the carbon atom to which the hydroxyl group is attached. Thus we find primary alcohols (VI and VII) in which two hydrogen atoms are left attached to the carbon ( $\text{CH}_2\text{OH}$ ), a secondary alcohol (VIII) in which one hydrogen atom is attached to the carbon ( $=\text{CHOH}$ ) and a tertiary alcohol (IX) in which there is no further hydrogen left ( $\equiv\text{COH}$ ). The significance of the classification into primary, secondary and tertiary alcohols becomes evident on attempting to oxidize them. A tertiary alcohol has no further hydrogen atom to oxidize to a hydroxyl group, hence oxidation of it results in splitting the carbon chain. Oxidation of primary and secondary alcohols is still possible with the formation of an aldehyde (X and XI,  $-\text{CHO}$ ) and a ketone (XII,  $=\text{CO}$ ) respectively. Further oxidation of a ketone leads to a splitting of the carbon chain, but oxidation of an aldehyde can occur with the formation of an acid (XIII and XIV,  $-\text{COOH}$ ).

Oxidation of each carbon group may occur independently. For instance if we start with propane (XV) and oxidize it in three successive stages we may obtain two different substances, namely propionic acid (XVIII) or glycerol (XIX) depending on whether the oxidation takes place on the same carbon atom, so that propyl alcohol (XVI) and propyl aldehyde (XVII) intervene between propane (XV) and propionic acid (XVIII), or that the oxidation takes place on the three separate carbon atoms giving rise to glycerol (XIX).



In the case of glycerol we have a substance containing two primary alcohol and one secondary alcohol grouping. The properties of the various groups determine to a great extent the chemical behaviour of the substance.

Alcoholic hydroxyl groups seem to confer on the substance the character of a weak acid or a weak base. Thus alcohols can form salts with strong bases or with acids. The aldehydes are easily oxidized to the corresponding acid and they may be fairly easily reduced. The ketones are not themselves oxidized but they confer the property of being easily oxidized on a hydroxyl group which is attached to the carbon atom next to the ketone group. The acids form the series of fatty acids.

### Carbohydrates

The above synopsis of some of the properties of the aliphatic series of compounds serves as a basis for the chemical description of the carbohydrates. As mentioned earlier in this chapter the solution left, after removal of caseinogen, fat and lactalbumin from milks readily reduces an alkaline solution of a cupric salt. It does this because there is an aldehyde group contained in lactose which being easily oxidized reduces the cupric salt to the cuprous condition.

In brief the carbohydrates consist of a chain of alcohol groups such as is shown in glycerol (XIX), but with one of the alcohol groups oxidized so as to form either an aldehyde or a ketone group.

**Reactions for Reducing Sugars. Moore's Test.** On heating

a solution of sugar with an alkali the sugar is oxidized by the oxygen of the air to form a brown solution containing caramel with its characteristic smell. The colour and smell become accentuated by the addition of strong sulphuric acid.

*Trommer's Test.* On adding to a solution of sugar some copper sulphate solution and alkali instead of the blue-green precipitate given by copper sulphate and alkali alone a deep blue solution is formed. This property of keeping cupric hydroxide in solution apparently depends upon the presence of alcoholic hydroxyl groups in the sugar. Glycerol and tartaric acid are examples of substances which possess the same power of keeping cupric hydroxide in solution although they are not sugars.

On heating cupric hydroxide it loses water and forms a black precipitate of cupric oxide. On heating the deep blue solution formed by the addition of copper sulphate and alkali to a reducing sugar, the sugar is oxidized. Oxidation of the sugar is accompanied by the reduction of the cupric hydroxide to cuprous hydroxide which forms a yellow precipitate and the cuprous hydroxide is dehydrated to cuprous oxide, and the precipitate becomes red. Frequently the yellow stage is so transient that it is not easily observed.

Many other reduction tests are used both for qualitative and quantitative purposes. An interesting application of the reduction by sugar is to deposit silver on glass to form a mirror by the reduction of an ammoniacal solution of silver nitrate.

*Fehling's Solution* is a mixture of a solution of copper sulphate (solution A) with an equal volume of an alkaline solution of a tartrate (solution B). The tartrate keeps the cupric hydroxide in solution, hence this reagent has the advantage that with excess of the reagent no black precipitate is mixed with the red precipitate, hence it is easier to recognize the reduction. On the other hand it has the disadvantage that with Trommer's test the formation of a clear blue solution may give a hint that a carbohydrate is present, although no reduction occurs. Other substances may give a clear blue solution, e.g. glycerol and ammonia, but any substance which produces a clear blue solution with Trommer's test should be tested for non-reducing carbohydrates.

*Benedict's Solutions* are used, one for qualitative and the other for quantitative tests. By the use of sodium carbonate instead of hydroxide the sugar is destroyed less rapidly, therefore a positive reaction may be given with weaker solutions of sugar. By means of potassium ferrocyanide and thiocyanate a white cuprous salt is formed; hence for quantitative work the end point of the disappearance of the blue colour is more easily observed.

*Nylander's test* is comparable to Fehling's test, but with a bismuth

salt in place of copper. On reduction by means of a sugar a black precipitate results.

*Picric Acid.* An alkaline solution of picric acid is reduced by heating with a sugar giving a red colour (picramic acid).

*Dyes.* Alkaline solutions of some dyes are altered by reduction; thus methylene blue is decolorized on heating with an alkaline sugar solution.

It must be noted that although other substances may have the power of reducing the various solutions described above those mentioned are convenient tests, some of which are more specific than others. That these reactions are due to compounds consisting of alcohol groups with either an aldehyde or a ketone group in the molecule has been mentioned previously. Many substances correspond to the above description, but most of the carbohydrates with which we have to deal are derivatives of chains of six carbon atoms, which are therefore called hexoses.

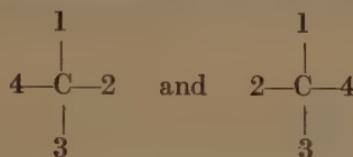
If we represent a chain of six carbon atoms each of which has attached to it one alcoholic hydroxyl, we see that it is only the end carbon atoms which form primary alcohols, therefore oxidation to an aldehyde can occur at either of the two end carbon atoms. There are, however, four intermediate carbon atoms which can form secondary alcohol groups and be oxidized to ketones, but we find that it is always the secondary alcohol group next to one of the end primary alcohol groups which is oxidized to form the ketone.

There is a general reaction which distinguishes the aldehyde sugars (aldoses) from the ketone sugars (ketoses). This is a red colour produced on heating with Seliwanoff's reagent.

*Seliwanoff Reaction.* Heat the solution with sufficient hydrochloric acid to form an 18 per cent. solution of hydrochloric acid and add a trace of resorcinol. Ketone sugars give a dark red solution with perhaps a red precipitate. The red precipitate dissolves in alcohol to form a red solution.

As soon as we attempt to consider this subject further we meet with a complication, namely the meaning of formulæ to represent the structure of organic chemical compounds. We have represented formulæ as lying in the plane of the paper with dashes for the bonds uniting the various atoms and groups. If we think of the subject at all we must realize that these represent three dimensional models only represented in a plane for convenience. If we confine our attention to compounds of carbon we can show that so long as there are no more than three different kinds of groups united to one carbon atom one formula will fit all possible arrangements of the groups in relation to the carbon atom. If, however, four different groups are attached to one carbon atom two different modes of linking the groups occur so that no possible turning of the two models built

to represent these linkages can make them coincide. Whenever such alternative formulæ are possible we find a condition known as asymmetry. The two formulæ are related to each other as the image of an object is to the object or as the right hand to the left hand of a pair of gloves. They are similar but inverted in the order of arrangement of the groups. Represented as projected on a plane surface the relationship can be thus expressed :



Where 1, 2, 3 and 4 represent four different groups.

#### THE EFFECT OF ASYMMETRY IN RELATION TO POLARIZED LIGHT

When light passes from one medium to another it is refracted. With certain materials a peculiar splitting of the light occurs so that two beams are formed which pass through the crystal in directions slightly divergent. Thus viewing objects through such a crystal as Iceland spar gives two images of the object looked at because two bundles of rays reach the eye by different paths. The splitting of the light into two rays is accompanied by a peculiar change in the vibration of the light waves. Normal light waves are regarded as vibrating radially (Fig. 81 A) in relation to the axis of their direction, but the light after passing through a doubly refractive medium is found to be so altered that the radial motion has been resolved into two vibrations at right angles to each other (Fig. 81, B and C). In the crystal, one, the ordinary ray is vibrating up and down as indicated by the cross lines, and the other, the extraordinary ray is vibrating perpendicularly to the surface and is represented end on as dots.

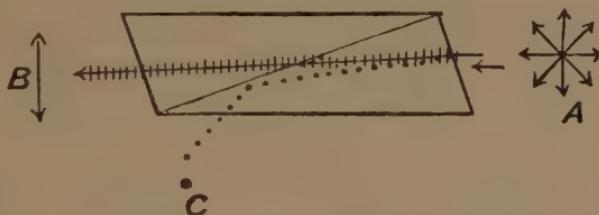


FIG. 81.—Diagram of the Course of Light through a Nicol's Prism.

At A a ray of light is represented facing the reader. If such a ray entered the prism in the direction of the arrow it would be polarized in two planes at right angles. One ray would vibrate vertically. This is shown by the line with dashes across it and by the arrow B. The other ray would vibrate horizontally at right angles to the paper. This ray becomes totally reflected and it is represented by dots. The end of a path of vibration is shown at C.

One ray is excluded by a device known as a *Nicol* prism which is formed by cutting a crystal of Iceland spar at a certain angle and cementing the two portions by a medium of appropriate re-

fractive index (Canada balsam). Owing to the refractive indices being different for the two rays the angle of the cut and the refractive index of the Canada balsam is such that one of the rays is totally reflected, whilst the other passes through undeflected. If the ray which has passed through such a prism falls on a second Nicol prism, it will be split up as was the original ray, only the proportion of the ray which passes by the different paths depends on the resolution of the ray into two rays at right angles to each other.

If the second prism is placed so that the direction of vibration of the ray is that which can pass through the prism all the light passes through the prism. If the direction of vibration is at right angles to that which can pass through the prism no light will pass through, as a vibration in one plane has no component at right angles to itself.

Intermediate angles will allow an intermediate amount of light to pass through depending upon the angle that the axes of the two prisms make with one another.

As it is extremely difficult to measure the amount of light which passes through the prism devices are employed by which the visual field is split into two or more areas such that these areas will match in luminosity at certain relative positions of the two prisms. Such an instrument is known as a polarimeter.

It has been necessary to describe this instrument because solutions of substances containing asymmetric carbon atoms rotate the plane of polarized light. Thus a beam which may be represented as vertical may be rotated through a certain angle. When analysed by a second prism the areas into which the visual field had been subdivided will now fail to match. If the original position is marked as zero and the second prism is rotated until the two fields match, the angle through which the second prism must be rotated in order to make the fields match is the angle by which the solution has rotated the polarized light. The extent of rotation must depend upon the strength of the solution and the distance that the light must travel through it. By convention the specific rotation of a substance is expressed by the formula

$$[\alpha]_D = \frac{\alpha \times 100}{c \times l}$$

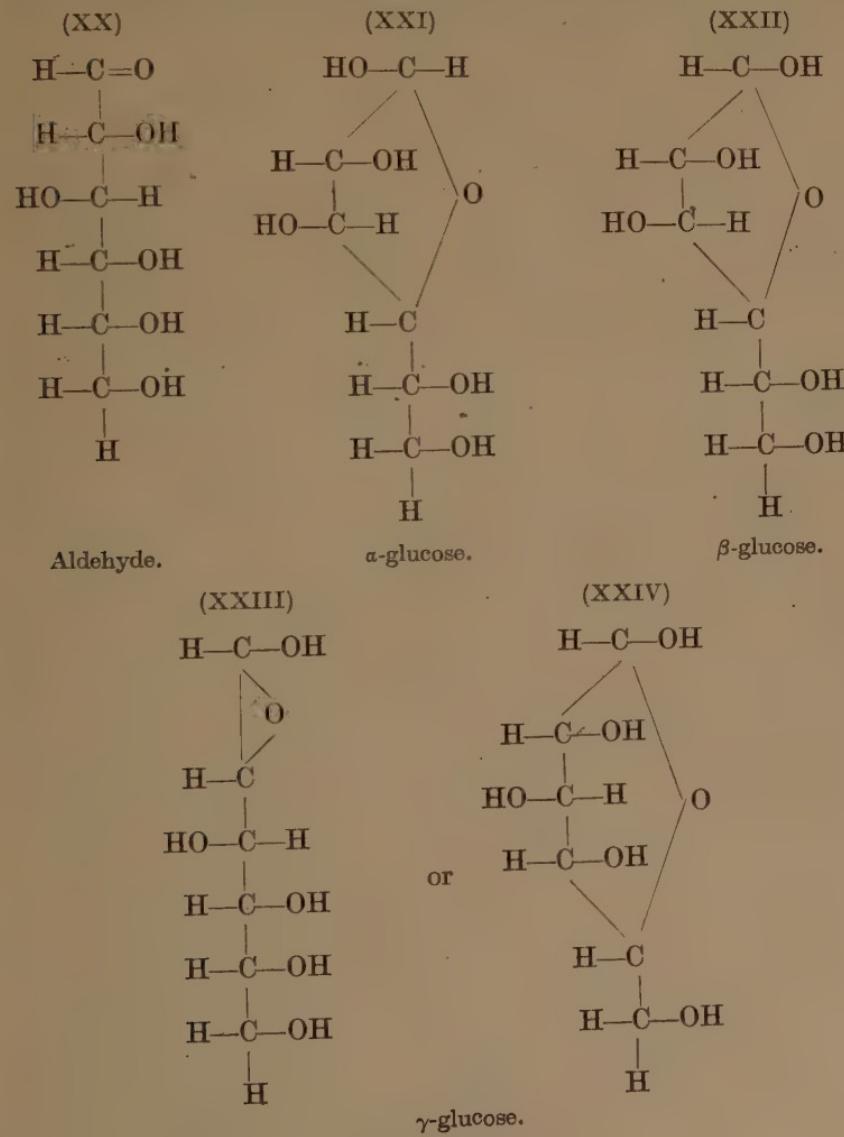
in which  $[\alpha]_D$  = the specific rotation of the substance in light from a sodium flame,  $\alpha$  = observed angle of rotation,  $c$  = concentration of the solution in per cent., and  $l$  = length of the tube in decimetres.

Returning now to the formula of a hexose we see that there are four asymmetric carbon atoms in an aldose and three in a ketose.

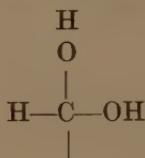
The permutations of the possible arrangement of the groups on these carbon atoms give rise to sixteen ( $2^4$ ) different compounds, most of which have been synthetized, but fortunately there are only three hexoses which must be considered in relation to physiological processes.

In addition to simple chains it is possible for ring formulae to occur. These are formed by the linkage of two carbon atoms through an oxygen atom.

**d-Glucose.** A solution of this hexose is less reactive than one would expect from the straight chain aldehyde, XX.



It has been found that two forms of glucose can be isolated in various ways. From analogy with the methyl-glucosides these have been termed  $\alpha$ - and  $\beta$ -glucose respectively (XXI and XXII). The former in solution has a specific rotation of  $+110^\circ$ ; after a time the rotation decreases until it becomes steady at  $+52.7^\circ$ . The latter has a specific rotation of  $+19^\circ$  which rises slowly to  $52.7^\circ$ . This is called muta rotation and equilibrium is more rapidly established after the addition of a trace of alkali. These two reach a condition of tautomeric equilibrium possibly through the open chain form, the aldehyde being in the form of aldehydrol, i.e. the top carbon atom in XX being hydrated to form



hence the lower reactivity than should occur with an aldehyde. The  $\alpha$ - and  $\beta$ -forms have a ring structure of the nature of a butylene oxide. The equilibrium state in dilute solution is about 37 per cent  $\alpha$ -glucose and 63 per cent.  $\beta$ -glucose. There are more reactive forms of glucose known as  $\gamma$ -glucose. They reduce an alkaline solution of permanganate in the cold. The formula of  $\gamma$ -glucose may be either that of an ethylene oxide (XXIII) or amylene oxide, (XXIV), probably the latter.

As described in the preceding paragraphs a solution of glucose is an equilibrium condition between the  $\alpha$  and  $\beta$  varieties. It is an aldose as it contains a potential aldehyde group. It reduces the various solutions described earlier in this chapter. Its specific rotation is  $+52.7^\circ$ . In order to distinguish it from other sugars the reaction with phenyl hydrazine is employed. Many of the sugars are so soluble that it is difficult to isolate crystalline derivatives. Emil Fischer introduced phenyl hydrazine as a reagent for sugars. On heating a solution of phenyl hydrazine with a sugar a complicated series of reactions occur which can be described as taking place in three stages.

Stage 1. Phenyl hydrazine replaces an oxygen which is united by two bonds to a carbon atom forming a phenyl hydrazone.

Stage 2. Another portion of phenyl hydrazine is reduced with the concomitant oxidation of an alcohol group. The group that is oxidized is that next to the one to which phenyl hydrazine was united in stage 1.

Stage 3. A further union of phenyl hydrazine to the sugar occurs so that two molecules are united to the sugar and an insoluble crystalline substance is formed: these are called phenyl osazones.

The crystalline osazones can be recognized by the melting points of the crystals or by their shape when viewed under the microscope. They are all canary yellow in colour.

Phenyl glucosazone melts at 205° C. and is recognized as long needles arranged in the shape of a radiating fan or as a double fan forming bundles like sheaves of corn.

**d-Fructose.** This is a ketone sugar, hence it gives Seliwanoff's reaction. It is very soluble and difficult to crystallize. It gives the reduction tests just as glucose does. Its specific rotation is —93°. It forms an osazone identical with that of glucose. The reason for the similarity of the osazones is that glucose and fructose are the same except for the two end carbon groups. If we represent

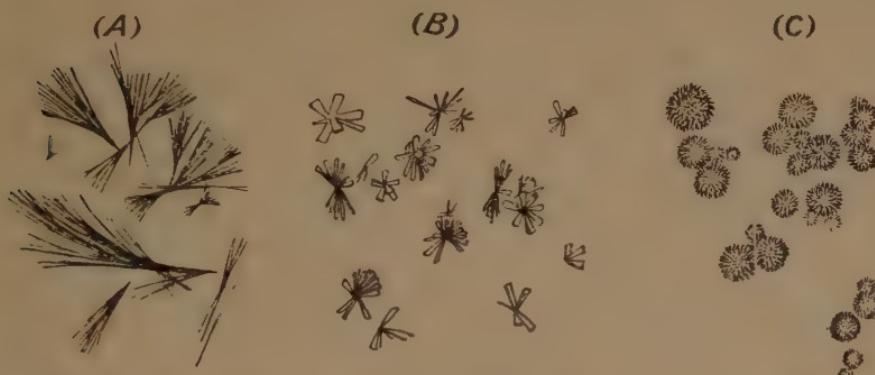
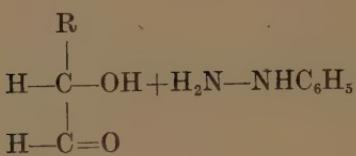


FIG. 82.—(A) Crystals of Phenyl Glucosazone ( $\times 40$ ). (B) Crystals of Phenyl Maltosazone ( $\times 40$ ). (C) Crystals of Phenyl Lactosazone ( $\times 40$ ).

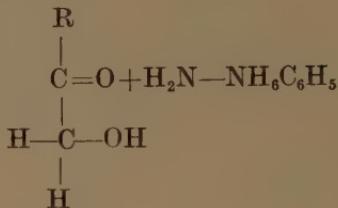
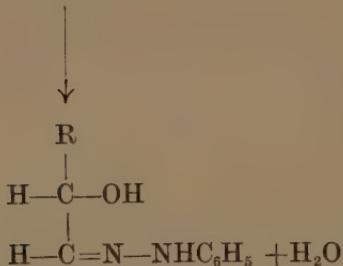
the process of osazone formation on these two groups the formulæ on page 120 explain the result.

**d-Galactose.** This sugar also gives the reduction tests like glucose and fructose. Its specific rotation is +83°. It forms an osazone (m.p. 190–193° C.) which somewhat resembles glucosazone. An interesting effect of the molecular structure is that on oxidation with nitric acid galactose gives rise to an insoluble acid (mucic acid, m.p. 213° C.), whilst glucose and fructose are oxidized to soluble acids. This *mucic acid test* is characteristic of galactose.

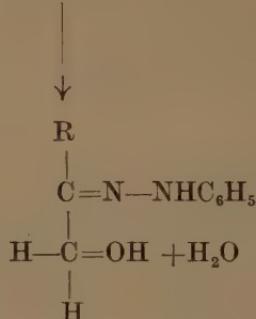
These three hexoses or monosaccharides are the main simple sugars. From them are formed more complicated carbohydrates. Two monosaccharides by uniting form compounds containing twelve carbon atoms known as dihexoses or disaccharides. The linkage of two hexoses is accompanied by the loss of a molecule of water—hence it is known as condensation or dehydration. The reverse process of splitting up disaccharides into monosaccharides with the addition of one molecule of water is known as hydrolysis.



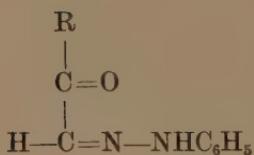
Glucose.



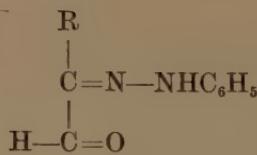
Fructose.



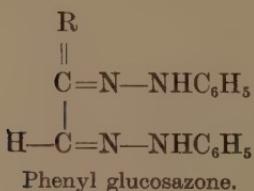
Oxidation.



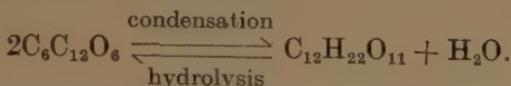
Oxidation.



By action of a further  
molecule of phenyl-  
hydrazine



This may be represented thus :—



The three disaccharides which are important in physiology, with the monosaccharides, which they yield on hydrolysis are—

**Maltose** (malt sugar) → 2 molecules of glucose.

**Lactose** (milk sugar) → 1 molecule of glucose + 1 molecule of galactose.

**Sucrose** (cane sugar) → 1 molecule of glucose + 1 molecule of fructose.

By linking the monosaccharides to form disaccharides the activity of the aldehyde and ketone groups is decreased. Thus a solution of cupric acetate in dilute acetic acid (*Barfoed's reagent*) is reduced by monosaccharides but not by disaccharides. In the case of sucrose all reducing power is lost.

**Maltose.** This reduces all the alkaline solutions of metallic salts. Its specific rotation is +138° C. Its osazone forms spherical rosettes of fusiform crystals (m.p. 206° C.).

**Lactose.** This likewise reduces alkaline solutions of metallic salts. Its specific rotation is +52.5° C. Its osazone forms spherical masses of hair-like crystals. The crystals are so fine that the masses may look like small balls and the presence of crystals can be recognized only by a faint striation at the edges of the masses of crystals. Owing to the presence of galactose it gives a mucic acid reaction.

**Sucrose.** This does not possess reducing properties, nor does it form an osazone. By hydrolysis it is converted into monosaccharides which possess reducing powers. Its specific rotation is +66.5°. Owing to the presence of fructose it gives the Seliwanoff reaction.

By further condensation so that several monosaccharide groups are united to form a larger molecule polysaccharides are formed. These have no reducing action, nor do they form osazones. By hydrolysis they are converted into the reducing sugars.

**Starch.** This is an insoluble powder which forms a gelatinous mass when heated in water. It gives a dark blue-black colour with iodine. Its specific rotation is + 199°. Starch is of great economic importance because it is the main form in which carbohydrate is stored in plants. It is readily precipitated by such substances as alcohol, and salts.

**Glycogen.** This is the form in which carbohydrates are stored in animals and in yeasts. It dissolves in water to form an opalescent

solution. It gives a mahogany brown colour with iodine. Its specific rotation is + 196·6°.

**Dextrins** are intermediate substances formed in the hydrolysis of starch or glycogen to hexoses. There are two main divisions of dextrins, namely those that give a reddish-brown colour with iodine and those which show no change of colour with iodine. The former are called erythrodextrins and the latter achroodextrins. The specific rotation of erythrodextrin is + 195°.

The distinguishing feature of erythrodextrin is that it differs in solubility from glycogen.

Glycogen is precipitated from its solution by 60 per cent. alcohol, by saturation with ammonium sulphate or by basic lead acetate. Dextrin is not precipitated by alcohol until the concentration of alcohol is over 90 per cent. It is not completely precipitated by saturation with ammonium sulphate and with basic lead acetate it is not precipitated unless ammonia is added, when it is precipitated just as any other carbohydrate would be precipitated under the same circumstances.

**Inulin** is a polysaccharide which is stored in some tubers. It is a derivative of  $\gamma$ -fructose.

The carbohydrates are fermented by micro-organisms, but the different kinds of organisms have selective activities in relation to the different carbohydrates. For example, lactose is not fermented by baker's yeast.

**Inosite** is not a carbohydrate although it is called "muscle sugar." It is a cyclic compound which is not fermentable by yeast, does not reduce Fehling's solution, nor does it rotate the plane of polarized light.

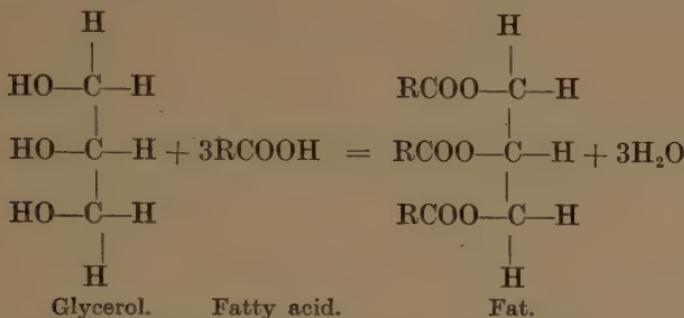
**Pentoses.** In addition to the carbohydrates with six carbon atoms to each molecular group there are some composed of five carbon atoms. They give special osazones, and they reduce alkaline solutions of metallic hydroxides. They give a special colour reaction for carbohydrates containing an odd number of carbon atoms.

A solution of a pentose, with an equal volume of concentrated hydrochloric acid, is heated in the presence of phloroglucinol. A cherry-red colour is produced, followed by a red precipitate. The red precipitate dissolves in amyl alcohol to give a red solution with an absorption band in the spectrum between D and E.

A less delicate reaction is given with orcinol, the colour changes from violet to blue-green or blue. The amyl alcohol solution shows an absorption band between C and D. Bial's reagent, which contains ferric chloride in addition to orcinol, is more delicate than orcinol alone.

### The Fats

These are compounds consisting of glycerol united with three molecules of fatty acid.



The chemical nature of glycerol and the formation of the acid group ( $\text{COOH}$ ) by the oxidation of a primary alcohol has been described above (p. 111). The characteristic of the fatty acids is that they consist of a chain of  $\text{CH}_2$  groups with a carboxyl group at one end and a hydrogen at the other as represented below :—



Thus all of them behave as acids, being able to combine with bases to form salts (soap). The fatty acids differ in physical properties depending on the number of the carbon atoms in the chain. The simplest acids (formic and acetic) are liquid, volatile substances freely soluble in water. With increasing number of carbon atoms their melting point is raised and they are less soluble in water ; thus the higher fatty acids are solid substances insoluble in water but soluble in such solvents as ether, chloroform, alcohol, etc.

Some of the fatty acids are deficient in two or more hydrogen atoms, so that two neighbouring carbon atoms are united by a double bond (unsaturated compound). This double bond does not indicate a firmer union between the two carbons, but is in fact a weak link where splitting of the chain into two chains may occur. The decrease in hydrogen atoms affects the chemical and physical properties of the fatty acids.

Unsaturated compounds readily absorb other elements, thus bromine and iodine are readily absorbed, forming halogen compounds ; in fact the amount of iodine absorbed is used as a measure of the degree of unsaturation of a compound. Unsaturated com-

pounds also absorb oxygen, and this reaction is used for the histological recognition of fats. Osmic acid is reduced by unsaturated fatty acids to a black precipitate which can be recognized under the microscope.

The physical characteristics of unsaturated fatty acids are that they have lower melting points and are more soluble than the corresponding saturated fatty acids.

The fats themselves are insoluble in water but soluble in ether, etc. They form greasy stains on polished surfaces, or make transparent marks on thin (cigarette) paper. Their chemical reactions depend on the glycerol and the fatty acids contained in them.

Glycerol is dehydrated by heating with dehydrating substances, such as potassium acid sulphate, giving rise to the volatile aldehyde acrolein, which can be recognized by its smell or by its ability to reduce an alkaline solution of silver to form a black stain on filter paper.

The fatty acids can be set free by hydrolysis, and their properties as acids insoluble in water and capable of replacing carbonic acid from its salts can be investigated. The unsaturated fats, because of the unsaturated fatty acids contained in them, absorb other elements such as halogens and oxygen. They are more soluble in hot alcohol than the corresponding saturated fats, and the soaps formed from them are more soluble than the soaps formed from the corresponding saturated acids.

The most common fats are those containing the three acids *palmitic*, *stearic* and *oleic* acids. Palmitic acid is represented by the formula  $C_{15}H_{31}COOH$ . Stearic acid contains two more  $CH_2$  groups, being represented by the formula  $C_{17}H_{35}COOH$ . Oleic acid is an unsaturated acid with the same number of carbon atoms as in stearic acid: its formula is  $C_{17}H_{33}COOH$ . Various other fatty acids are found in animal fats. Some are more unsaturated than the oleic acid series.

Chemical investigation of a fat commences by a determination of certain "values."

The *acid value* is measured by direct titration of a warm alcohol solution of the fat by alkali, using phenol phthalein as an indicator. It shows the amount of free fatty acid in the mixture.

The *saponification value* is measured by boiling the fat with an alcoholic solution of potassium hydroxide. The fat is saponified, i.e. hydrolyzed to glycerol and fatty acids. The fatty acids combine with the alkali to form soaps. A portion of the original alcoholic potash is titrated in the presence of phenol phthalein. The mixture of saponified fat is also titrated, using the same indicator. The difference between the amount of alkali added and that found after hydrolysis is a measure of the total amount of fatty acid in the fat.

The *Reichert-Meissl value* is a measure of the volatile fatty acids

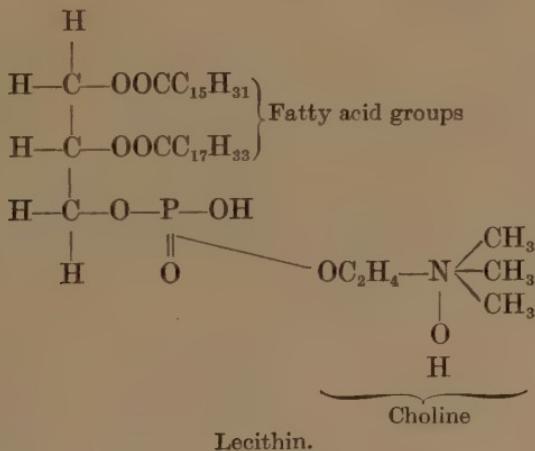
in a fat. The fat is saponified; the solution is acidified, and it is distilled in a current of steam. The distillate is titrated with alkali in the presence of phenol-phthalein. The importance of this test is that butter contains a fair amount of volatile fatty acids.

The *iodine value* shows the degree of unsaturation of the fat. Olive oil contains a fair amount of oleic acid. The fat is dissolved in a solvent such as chloroform and a solution of iodine is added to it. After a definite period of time the excess of iodine is determined by titration with thiosulphate using starch as an indicator for iodine. The amount of iodine which disappears during the process is the measure of the iodine value.

### Lipins

Fatty acids may unite with other substances besides glycerol. Cerebrosides are compounds of galactose with fatty acids and with the nitrogenous base sphingosine. These substances are soluble in fat solvents, hence extracts of tissues contain them as well as fats. The general term **lipin** includes all these substances.

**Lecithin** is formed by the union of two molecules of fatty acid with glycerol. The third alcohol hydroxyl is united to phosphoric acid which in turn combines with a nitrogenous base which is usually choline.



**Cholesterol** is a secondary alcohol belonging to the terpene series. It is widely distributed in all kinds of cells. It forms the greater part of what is called the unsaponifiable matter of fats. It has the properties of an unsaturated substance. It is also found combined with fatty acids to form cholesterol esters. Cholesterol crystallizes from alcohol in the form of flat plates with an indented corner and it can be estimated by the precipitation of an insoluble compound with digitonin. It gives certain colour reactions, of

which *Salkowski's* reaction is the best known. A dry chloroform solution of cholesterol is shaken with concentrated sulphuric acid.

The chloroform solution becomes coloured red.

*Liebermann's Reaction*.—Dissolve cholesterol in chloroform and add several drops of acetic anhydride. On adding concentrated sulphuric acid drop by drop a red colour appears which later becomes blue or bluish green.



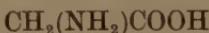
FIG. 83.—Cholesterol Crystallized from Alcohol.

Redrawn from a Photomicrograph. (Roaf, *Bio-logical Chemistry*, Methuen & Co.).

ammonia group is united to form an amine: the simplest being glycine, the amino derivative of acetic acid.



Acetic Acid.



Glycine or amino acetic acid.

By this union the molecule contains an acid group (COOH) and a basic group ( $\text{NH}_2$ ). These interfere with each other so that in solution the amino acid is neutral, but it can combine with base or acid when either is added. Thus the amino acids are known as amphoteric substances. Some amino acids have more than one carboxyl group or more than one amino group: the former are more acid and the latter more alkaline than the normal amino acids. The reactions of the amino acids depend on the chemical groups which are united to the amino acid group.

Table VII shows that in nearly every case the amino group is in the  $\alpha$  position—that is, it is attached to the carbon atom next to the carboxyl group. Where more than one amino group is present the second one is at the far end from the carboxyl group. It requires a great deal of skill to separate these amino acids from proteins, but we can study certain properties without actually isolating them.

**Colour Tests.** Certain colour tests for proteins depend upon the presence in them of special amino acids.

*Xanthoproteic Reaction*.—Heating an amino-acid containing an aromatic ring with dilute nitric acid produces a yellow nitro-benzene derivative which on the addition of an alkali becomes orange.

### The Proteins

The proteins are composed of a number of nitrogen-containing molecules known as the amino acids. Each amino acid consists of a fatty acid to which an am-

TABLE VII  
LIST OF AMINO ACIDS

*Mono amino monocarboxylic acids*

Glycine or  $\alpha$ -amino acetic acid.  $\text{CH}_2(\text{NH}_2)\text{COOH}$ .

Alanine or  $\alpha$ -amino propionic acid.  $\text{CH}_3\text{CH}(\text{NH}_2)\cdot\text{COOH}$ .

Serine or  $\beta$ -hydroxy- $\alpha$ -amino propionic acid.  $\text{CH}_2\text{OH}\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH}$ .

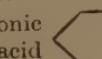
Cysteine or  $\beta$ -thio hydroxy- $\alpha$ -amino propionic acid,  $\text{CH}_2\text{SH}\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH}$ .  
two molecules of which unite to form cystine.  $[-\text{SCH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH}]_2$

Valine or  $\alpha$ -amino-iso-valeric acid.  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 > \text{CH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH} \end{array}$

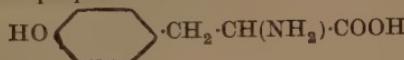
Leucine or  $\alpha$ -amino-iso-butyl acetic acid.  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 > \text{CH} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH} \end{array}$

Isoleucine or  $\beta$ -methyl- $\beta$ -ethyl- $\alpha$ -amino pro- $\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}_2\text{H}_5 > \text{CH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH} \end{array}$   
pionic acid

*Aromatic amino acids*

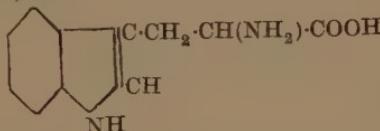
Phenylalanine or  $\beta$ -phenyl- $\alpha$ -amino propionic acid 

Tyrosine or  $\beta$ -parahydroxyphenyl- $\alpha$ -amino propionic acid

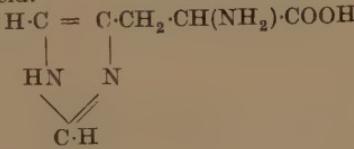


*Heterocyclic amino acids*

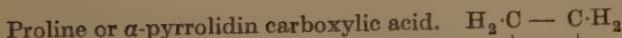
Tryptophane or  $\beta$ -indole- $\alpha$ -amino propionic acid



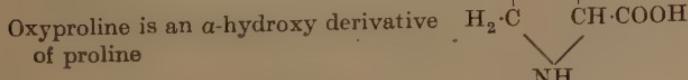
Histidine or  $\beta$ -iminoazole- $\alpha$ -amino propionic acid.



Proline or  $\alpha$ -pyrrolidin carboxylic acid.

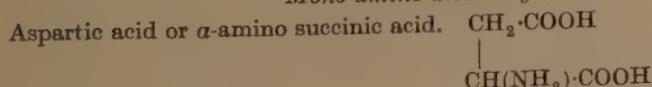


Oxyproline is an  $\alpha$ -hydroxy derivative of proline

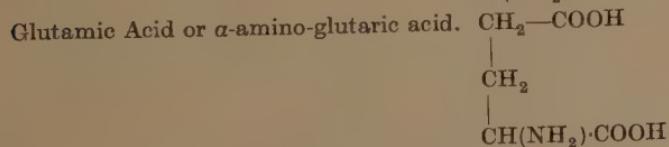


*Mono-amino-dicarboxylic acids*

Aspartic acid or  $\alpha$ -amino succinic acid.

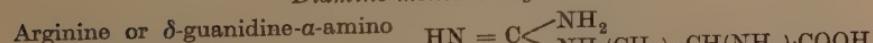


Glutamic Acid or  $\alpha$ -amino-glutaric acid.

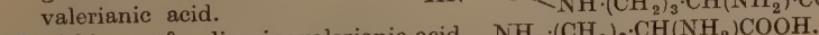


*Diamino-monocarboxylic acids*

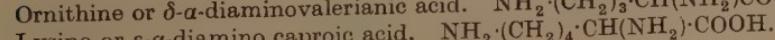
Arginine or  $\delta$ -guanidine- $\alpha$ -amino valeric acid.



Ornithine or  $\delta$ - $\alpha$ -diaminovaleric acid.



Lysine or  $\epsilon$ - $\alpha$ -diamino caproic acid.



*Tyrosin Reaction.* Heating an amino-acid containing a phenol group with Millon's Reagent produces a red colour. The amino acid containing this group is tyrosin.

*Tryptophane Reaction.* On adding a solution of glyoxylic acid to a solution of tryptophane, then floating the mixture on concentrated sulphuric acid, a purple ring is produced at the junction of the two. This reaction is given by proteins containing tryptophane. A similar reaction is given using formaldehyde instead of glyoxylic acid.

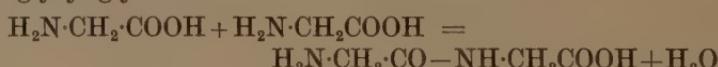
*Sulphur or Cystine Reaction.* A protein containing cystine when heated with alkali liberates hydrogen sulphide which in the presence of lead acetate produces a black or brown colour due to lead sulphide.

Phospho-tungstic and phospho-molybdic acids precipitate the diamino acids. This precipitation is used in Hausmann's method for characterizing proteins.

Free NH<sub>2</sub> groups can be decomposed by the action of nitrous acid with the liberation of nitrogen as a gas. This method is used by Van Slyke for the differentiation of proteins.

These two methods will be described after we know something more about the structure of proteins.

**Peptide Linkage of Amino Acids.** Amino acids can be united by combining the amino group of one with the carboxyl group of another. For example, two molecules of glycine can combine to form glycyl-glycine



This is a process of condensation with loss of water : the reverse process of hydrolysis causes the splitting of the di-peptide into its constituent amino acids. Long chains of amino acids may be united

to form polypeptides, in which the characteristic group O=C—NH— is repeated at each linkage. A number of these groups in the same molecule gives rise to a colour reaction with copper sulphate and alkali. The colour varies from pink to purple as the complexity of the compound increases. As a similar pink colour is given by biuret with copper sulphate and alkali it is therefore called the *biuret (Rose) reaction*.

With increasing molecular weight the solubility of the proteins decreases and we find that many reagents precipitate them from their solutions. The groups of precipitants are :—

*Strong Mineral Acids :* Hydrochloric, sulphuric and nitric acids.

*Alkaloidal Reagents :* Bromine water, trichloracetic acid, potassium-mercuric iodide, phospho-tungstic acid, tannic acid, etc.

*Metallic Salts :* Copper, lead, mercury, silver, etc., salts.

*Neutral Salts :* Strong or saturated solutions of sodium chloride,

ammonium sulphate, magnesium sulphate, etc., alcohol, acetone, etc.

In several cases a coagulation on boiling their neutral solution is a most distinctive reaction.

The proteins have been classified according to these various reactions, but it must be remembered that the colour reactions for special amino acids depend on the nature of the amino acids in the molecule and not on the group to which the protein belongs.

#### CLASSIFICATION AND SPECIAL DISTINCTIVE PROPERTIES OF PROTEINS

1. *Protamines* are simple basic substances which can be precipitated from their solutions by ammonia. They are mainly derived from fish-sperm.

2. *Histones* are similar to but slightly more complex than the protamines. Globin derived from haemoglobin is an important member of the group.

3. *Sclero-proteins* are derived from skeletal structures. Gelatin is the commonest example and it is characterized by the absence of aromatic amino acids and by the property of forming a jelly (gel) in water.

4. *Phospho-proteins* contain phosphorus in a form which is easily spit off, by dilute alkalies, as phosphoric acid. Caseinogen and vitellin are the chief examples. They are precipitated by dilute acetic acid.

5. *Albumins* are coagulated on heating. They dissolve in distilled water and are precipitated from solution by complete saturation with ammonium sulphate.

6. *Globulins* like the albumins are coagulated on heating. They do not dissolve in distilled water, as they require some salt to be present. They are, however, more easily precipitated from their solutions by neutral salts. They are precipitated for instance by half saturation with ammonium sulphate. A distinction is made between euglobulin, which is precipitated by dialysis and by half saturation with ammonium sulphate, and pseudoglobulin which is not precipitated by dialysis.

7. *Conjugated proteins* are those in which a protein is combined with a clearly defined "prosthetic" group.

(a) *Nucleo-proteins*. These contain nuclein (see p. 272), and they are derived from the nuclei of cells.

(b) *Gluco-proteins*. These contain a carbohydrate group. They give a well marked Molisch reaction. Mucin is an example of this group.

Both these groups are precipitated by weak acids, e.g. acetic acid.

(c) *Chromo-proteins* of which haemoglobin is the chief example (see p. 241).

TABLE VIII  
THE COMPOSITION OF SOME PROTEINS (PLIMMER)

|                         | Serum<br>Albumin<br>(Horse). | Serum<br>Globulin<br>(Horse). | Fibrin. | Caseinogen<br>(Cow). | Ox<br>Muscle. | Gelatin. | Gluten<br>(Wheat). | Gliadin<br>(Wheat). | Zein. | Globin<br>(Horse). |
|-------------------------|------------------------------|-------------------------------|---------|----------------------|---------------|----------|--------------------|---------------------|-------|--------------------|
| Glycine . . . . .       | 0                            | 3.5                           | 3.0     | 0                    | 2.1           | 16.5     | 0.4                | 0.0                 | 0.0   | —                  |
| Alanine . . . . .       | 2.7                          | 2.2                           | 3.6     | 1.5                  | 3.7           | 0.8      | 0.3                | 2.0                 | 9.8   | 4.2                |
| Valine . . . . .        | —                            | +                             | 1.0     | 7.2                  | 0.8           | 1.0      | —                  | 3.4                 | 1.9   | —                  |
| Leucine . . . . .       | 20.0                         | 18.7                          | 15.0    | 9.4                  | 11.7          | 2.1      | 4.1                | 6.6                 | 19.6  | 29.0               |
| Isoleucine . . . . .    | —                            | —                             | —       | —                    | —             | —        | —                  | —                   | —     | —                  |
| Phenylalanine . . . . . | 3.1                          | 3.8                           | 2.5     | 3.2                  | 4.5           | 2.2      | 0.4                | 1.0                 | 2.4   | 6.6                |
| Tyrosin . . . . .       | 2.1                          | 2.5                           | 3.5     | —                    | 0.8           | 0.5      | 0.0                | 1.9                 | 1.2   | 3.6                |
| Serine . . . . .        | 0.6                          | —                             | —       | —                    | 1.1           | ?        | 0.4                | —                   | 0.2   | 1.0                |
| Cystine . . . . .       | 2.5                          | 1.5                           | —       | —                    | —             | —        | —                  | —                   | 0.5   | —                  |
| Proline . . . . .       | —                            | 1.0                           | 2.8     | 3.6                  | 6.7           | 5.8      | 7.7                | 4.0                 | 13.2  | 9.0                |
| Oxyproline . . . . .    | —                            | —                             | —       | —                    | 0.3           | —        | 3.0                | —                   | —     | —                  |
| Aspartic Acid . . . . . | 3.1                          | 2.5                           | 2.0     | —                    | —             | 4.5      | 0.6                | 0.7                 | 0.6   | 1.7                |
| Glutamic Acid . . . . . | 7.7                          | 8.5                           | 10.4    | —                    | —             | 15.6     | 15.5               | 0.9                 | 24.0  | 43.7               |
| Tryptophane . . . . .   | —                            | —                             | —       | —                    | —             | —        | —                  | —                   | —     | —                  |
| Arginine . . . . .      | —                            | —                             | —       | —                    | —             | —        | —                  | —                   | —     | —                  |
| Lysine . . . . .        | —                            | —                             | —       | —                    | —             | —        | —                  | —                   | —     | —                  |
| Histidine . . . . .     | —                            | —                             | —       | —                    | —             | —        | —                  | —                   | —     | —                  |
| Ammonia . . . . .       | —                            | —                             | —       | —                    | —             | —        | —                  | —                   | —     | —                  |
| Total . . . . .         | 42.8                         | 48.0                          | 46.5    | 66.5                 | 67.5          | 44.6     | 46.7               | 83.8                | 85.4  | 69.7               |

Two special groups of vegetable proteins are also important because they form the sticky material of dough, and they are therefore important in the process of making bread.

8. *Glutelins* soluble in dilute alkalies.

9. *Gliadins* soluble in 70 per cent. alcohol.

**Hausmann's Method for Analysis of Proteins.** In order to learn something about the general nature of the various proteins the following method may be followed. Estimate the total nitrogen in the protein, then hydrolyze the protein by hydrochloric acid. Distil off the ammonia and estimate the percentage of the total nitrogen which is recovered as ammonia (Amide N.). Next precipitate, from the ammonia-free residue, the basic or diamino-acids by phospho-tungstic acid. Estimate the amount of nitrogen in the precipitate and express it as a percentage of the total nitrogen. Finally estimate the nitrogen of the monoamino acids which remain in the filtrate from the phospho-tungstic acid precipitate.

Van Slyke has modified this procedure by estimating the amine groups in the phosphotungstic acid precipitate and in the mono-amino acid solution by decomposing them with nitrous acid and measuring the amount of nitrogen given off as a gas.

In addition to the above fractions an insoluble pigmented precipitate usually occurs during hydrolysis. This precipitate is filtered off and the nitrogen contained in it is called "humin" nitrogen.

TABLE IX  
HAUSMANN NUMBERS OF SOME PROTEINS (PLIMMER)

|                          | Amide N. | Humin N. | Diamino N. | Monoamino N. | Total N. |
|--------------------------|----------|----------|------------|--------------|----------|
| Serum albumin . . . .    | 0.95     | 0.15     | 4.86       | 8.81         | 14.60    |
| Serum globulin . . . .   | 1.41     | —        | 3.95       | 10.81        | 16.17    |
| Gelatin . . . .          | 0.29     | —        | 6.45       | 11.26        | 18.00    |
| Glutelin (wheat) . . . . | 3.30     | 0.19     | 2.05       | 11.95        | 17.49    |
| Gliadin (wheat) . . . .  | 4.34     | 0.07     | 1.00       | 12.25        | 17.66    |
| Zein (maize) . . . .     | 2.97     | 0.16     | 0.49       | 12.51        | 16.13    |
| Hæmoglobin . . . .       | 1.07     | —        | 4.07       | 10.95        | 16.81    |

### Protein Derivatives

The amino acid linkages can be unlocked by hydrolysis just as the polysaccharides can be hydrolyzed to monosaccharides. In this process a series of simple protein-like bodies are formed. These are classified below and their characteristic properties tabulated. The colour reactions are dependent on the amino acids contained in the original protein. The proteins are represented as being either albumin or globulin, but such bodies as gelatin will pass through a similar series of stages when hydrolyzed.

TABLE X  
PROTEINS AND THEIR HYDROLYTIC PRODUCTS

| Substance.                         | Colour with<br><i>CuSO<sub>4</sub></i> and<br>Alkali. | Precipitation by<br><i>(NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub></i> | Distilled Water.                                  |
|------------------------------------|---|---|---|
| Albumin . . .                      | Purple  | At saturation   | Soluble   |
| Globulin . . .                     | Purple  | At half-saturation  | Not soluble : some salt necessary                 |
| Metaprotein . . .                  | Purple  | At half-saturation  | Not soluble : a trace of acid or alkali necessary |
| <b>Primary Proteoses :</b>         |   |   |   |
| (a) Heteroproteose                 | Pink  | At half-saturation  | Not soluble : some salt necessary                 |
| (b) Protoproteose .                | Pink  | At half-saturation  | Soluble   |
| Secondary or Deuteroproto-proteose | Pink  | At saturation   | Soluble   |
| Peptone . . .                      | Pink  | Not precipitated  | Soluble and dialyzable                            |
| Polypeptides . . .                 | Blue  | Not precipitated  | Soluble and dialyzable                            |
| Amino-Acids . . .                  | Blue  | Not precipitated  | Soluble and dialyzable                            |

### Composition of Foods

The three classes of chemical substances described above along with inorganic salts form the greater proportion of the foods taken into the body. Depending on the relative preponderance of one or other of these classes we recognize carbohydrate, fatty and protein foods.

It is not always so easy to separate the constituents of a food as in the example given of the separation of the constituents of milk. It is, however, possible to apply many of the qualitative tests described above to unseparated food materials.

Animal food products are in general protein foods : that is they contain a relatively high percentage of protein, but some of the animal foods are distinctly fatty in nature, for example butter and lard.

*Eggs* are divisible into two portions, white and yolk. The former is a solution of almost pure protein, but the yolk contains a large amount of fat. The yolk is the stored food material for the developing ovum just as milk is the food material for the newly-born mammal. The protein of the yolk is largely a phospho-protein, vitellin, which is thus comparable to the caseinogen of milk. Lecithin forms a large proportion of the fat in egg yolk.

Animal food products vary greatly in their composition. In Table XI are given a few selected examples.

The cereal foods are predominantly carbohydrate. They ought to consist of the seed, which includes the endosperm and germ with more or less of the coats surrounding these. In milling the coats are separated, forming bran and semolina. The germ is also removed, leaving the endosperm. The endosperm, which is composed mainly of starch, gives a whiter flour and one with better keeping qualities

than if the germ were included. Polished rice corresponds to white flour in that the coats and germ are removed during milling. On such white products as bread, rice, etc., it is possible to carry out tests for the constituents. A drop of iodine shows an intense black stain due to the large amount of starch present. Copper sulphate followed by alkali shows the purple colour of the biuret test for protein. Millon's reagent placed on the surface soon shows a brick-red colour without any heating, and nitric acid followed by ammonia shows the xanthoproteic reaction.

In addition to starch two special proteins are present in wheat, namely gliadin and glutelin. The former is soluble in 70 per cent. alcohol, but insoluble in water or absolute alcohol. It forms a sticky mass with water which causes the stickiness of dough. The glutelin is soluble in dilute alkalies.

Many seeds contain large stores of protein or fat. The former kind are represented by peas and beans belonging to the order of leguminosæ. From the latter are obtained such vegetable oils as almond and olive oil. In Table XI are also shown a few examples of vegetable food products.

TABLE XI

TABLE OF FOOD VALUES FROM ANALYSES AND ENERGY VALUES OF FOODS  
(R. H. A. PLIMMER)

|                               | Ash. | Protein. | Carbo-hydrate. | Fat.  | Calories per 100 gm. |
|-------------------------------|------|----------|----------------|-------|----------------------|
| <b>Animal Foods</b>           |      |          |                |       |                      |
| Beef (Fore-quarter) . . . . . | 0.93 | 18.84    | 0.0            | 18.39 | 248.3                |
| Mutton (Shoulder) . . . . .   | 0.76 | 13.24    | 0.0            | 34.91 | 379.0                |
| Pork (Shoulder) . . . . .     | 0.50 | 15.42    | 0.0            | 27.04 | 314.7                |
| Butter (Cornish) . . . . .    | 2.3  | 0.0      | 0.0            | 81.6  | 758.9                |
| Cheese (Cheddar) . . . . .    | 4.4  | 25.2     | 0.0            | 33.4  | 427.5                |
| <b>Eggs :</b>                 |      |          |                |       |                      |
| $\frac{2}{3}$ white . . . . . | 0.4  | 7.1      | 0.0            | 0.07  |                      |
| $\frac{1}{2}$ yolk . . . . .  | 0.7  | 5.2      | 0.0            | 11.19 |                      |
| Whole . . . . .               | 1.1  | 12.3     | 0.0            | 11.26 | 161.9                |
| Herrings (fresh) . . . . .    | 1.04 | 12.1     | 0.0            | 10.95 | 151.4                |
| <b>Vegetable Foods</b>        |      |          |                |       |                      |
| (a) Cereals :                 |      |          |                |       |                      |
| Wheat grain . . . . .         | 1.7  | 10.9     | 70.4           | 1.2   | 344.5                |
| Wheat flour . . . . .         | 0.5  | 11.1     | 76.1           | 1.3   | 371.6                |
| Bread . . . . .               | 1.8  | 7.2      | 48.1           | 0.2   | 228.6                |
| Oats, fine meal . . . . .     | 1.8  | 11.7     | 69.3           | 8.3   | 409.3                |
| (b) Fresh vegetables :        |      |          |                |       |                      |
| Beetroot . . . . .            | 1.3  | 1.2      | 6.2            | 0.10  | 31.3                 |
| Cabbage . . . . .             | 0.6  | 1.4      | 4.5            | 0.10  | 25.1                 |
| Potatoes . . . . .            | 1.7  | 2.1      | 19.0           | 0.05  | 87.0                 |
| (c) Pulses :                  |      |          |                |       |                      |
| Butter beans . . . . .        | 4.0  | 18.6     | 62.2           | 0.7   | 337.8                |
| Whole green peas . . . . .    | 2.7  | 20.4     | 57.1           | 0.6   | 323.3                |
| Soya beans . . . . .          | 4.5  | 33.7     | 32.5           | 18.3  | 441.6                |
| (d) Nuts with shell :         |      |          |                |       |                      |
| Almond (Jordan) . . . . .     | 3.2  | 22.0     | 15.5           | 52.2  | 639.2                |
| Brazil . . . . .              | 3.3  | 13.2     | 8.1            | 70.4  | 742.1                |

In cooking foods their physical conditions are altered.

Starch is hydrated by heating in the presence of moisture whereby the plastids in which the starch is contained are broken and the starch is more easily acted upon by the digestive juices.

Meat, which consists of muscle fibres bound together by connective tissue is softened by heating. In the presence of moisture the collagen of the connective tissue is converted into gelatin which is soluble in hot water. Therefore boiling meat causes the fibres to be more easily separated, that is it renders the meat "tender."

In making bread gas is formed by fermentation or gas is introduced by aeration. The gas is entangled in the sticky dough so that when the gas expands during heating, a spongy mass is formed. Coagulation of the proteins makes the spongy condition permanent. During fermentation some of the starch is converted into sugars and dextrin. Near the surface of the loaf the sugar, and possibly some of the dextrin, is converted into caramel which gives the brown colour and the taste to the crust (cf. Moore's test, p. 112).

Further details in relation to foods will be given later after we have considered the chemical aspects of the food supply.

## CHAPTER IX

### EXCRETORY PRODUCTS

#### The Urine

The food substances described in the preceding chapter are oxidized in the body. Most of the hydrogen and carbon are converted into water and carbon dioxide respectively. The carbon dioxide leaves the body mainly in the expired air and the water passes out through the lungs, skin, alimentary canal and kidneys. The nitrogenous substances are not completely oxidized and products of partial oxidation must be removed from the body. These end products pass through the kidneys into the urine.

As the urine is a solution containing a large number of comparatively simple substances a brief description of it will indicate the main end products of the oxidation of the nitrogen-containing food substances. After we know the nature of these substances we shall understand something of the problem to be solved in tracing the food substances into the body and the changes that they must undergo in being changed into the end products which pass out of the body.

We can start by a few simple tests in the same way that we started with a few simple experiments to separate the constituents of milk.

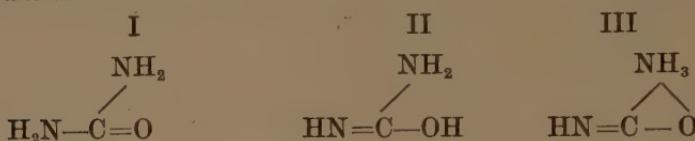
After adding a weak alkali, such as calcium carbonate, to urine a volatile base is given off. This can be proved by drawing an ammonia-free current of air through the urine into a dilute solution of sulphuric acid. This volatile base is *ammonia* and it may be measured quantitatively by titrating the acid into which it has been drawn by the air current. The presence of the volatile base may be shown by suspending red litmus paper above the alkaline urine.

If a stronger alkali is used and the solution is heated the amount of ammonia given off is greatly increased. This suggests that something of the nature of an amide is present. This amide-like substance is urea.

#### Urea

The structural formula for urea may be one of several forms, and it is possible that these are in tautomeric equilibrium in solution. Urea is often considered to be the diamide of carbonic acid (formula

I), but Werner has produced a large amount of evidence in favour of formulae II and III.

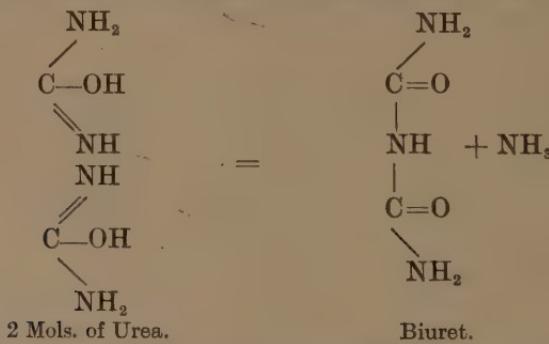


Urea crystallizes in long needles and such needles can be obtained by evaporating urine to dryness and extracting the residue with boiling acetone. The residue insoluble in acetone contains other nitrogenous substances to which we shall refer later in this chapter. Urea decomposes on heating with alkali giving rise to ammonia, showing a great similarity to the behaviour of urine in this respect.

A concentrated solution of urea treated *in the cold* with strong nitric acid (free from nitrous acid) gives crystals of urea nitrate. Human urine is too dilute to show this reaction, and it must be concentrated before the precipitation will occur, but dog's urine, which contains a larger amount of urea, gives a precipitate of urea nitrate without concentration.

Urea also forms a relatively insoluble oxalate so that if urine is saturated with oxalic acid (1 g. in 10 c.c.) crystals of urea oxalate will separate from the solution.

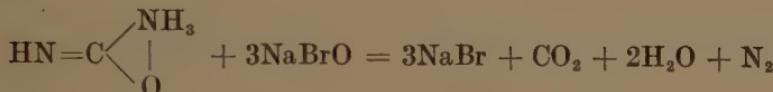
The reaction obtained by heating dry urea in a test tube is not of much use from a physiological standpoint, but it is of interest because of the similar colour test given by proteins. Urea when heated splits off ammonia and forms biuret. Biuret on addition of copper sulphate gives a pink colour. This is due to the  $\text{O}=\text{C}-\text{N}$  groups which occur in the peptide linkages (see p. 128).



A solution of urea is decomposed by nitrites, therefore in the preparation of urea nitrate nitrous acid must be avoided. This is a general reaction for  $\text{NH}_2$  groups and it has been applied in studying the  $\text{NH}_2$  groups in proteins and protein derivatives (see p. 128). Urea is decomposed by an alkaline solution of sodium hypobromite forming molecular nitrogen and carbon dioxide. The latter is

absorbed by the excess of alkali of the reagent : the nitrogen is set free as a gas. This gas can be measured and used as a basis for the quantitative estimation of urea.

Theoretically 1 g. urea should liberate 372 c.c. of Nitrogen at 0° and 760 mm. pressure, but practically only 354 c.c. are obtained. Other amide bodies give similar reactions, so the results obtained are not strictly accurate.



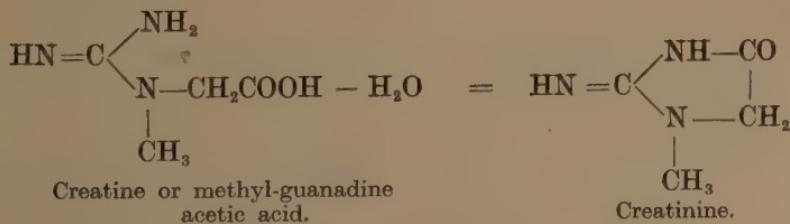
The most accurate method for the estimation of urea is to hydrolyze it to ammonium carbonate and to measure the amount of ammonia formed. The enzyme, urease, is used for the quantitative estimation of urea by hydrolyzing urea into ammonium carbonate.

Returning to the residue left after extracting dried urine with acetone it is possible to effect a further separation by extracting the residue with water. Part of the residue still remains insoluble but some of the constituents are dissolved. The solution contains inorganic ions which are mainly due to those contained in the food materials, but are partly derived by the formation of sulphates from sulphur and phosphates from phosphorus contained in the proteins. In addition to the salts there is a nitrogen-containing compound known as creatinine. It gives the two following colour reactions.

**Creatinine.** *Jaffe's Test.* Picric acid and alkali produce an orange colour with creatinine and the intensity of this colour is used for the colorimetric estimation of creatinine.

*Weyl's Test.* Sodium nitroprusside and alkali produce a red colour with creatinine. This red colour, which is similar to the red colour produced by the same reagents and acetone, can be distinguished as follows. On standing the red colour fades to yellow. If acetic acid is now added and the solution is heated it turns green. Finally the green changes to blue and a dark blue precipitate forms.

Creatinine is allied chemically to creatine. The structural formulae are

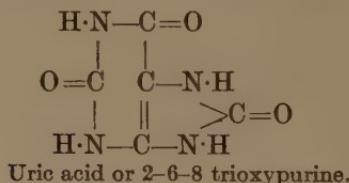


The final insoluble residue left after extracting dried urine with acetone and then with water gives an orange red colour when heated to dryness with nitric acid. This colour becomes purple with ammonia and blue with stronger alkalies. This is known as the murexide test and shows the presence of uric acid.

**Uric Acid.** Uric acid is a substance of low solubility in water but soluble in dilute alkalies. Its ammonium salt is insoluble, especially in the presence of excess of ammonium salts. When one wishes to make a quantitative estimation of uric acid, it is usually precipitated from its solution by ammonia and ammonium salts.

Uric acid gives a blue colour with phosphotungstic acid : this colour is used for the colorimetric estimation of uric acid. Phenols give a similar colour with phospho-molybdic acid ; they must therefore be removed before the estimation is made.

In addition to the murexide test and the colour reaction with phosphotungstic acid uric acid can reduce metallic salts. Prolonged boiling with Fehling's solution will sometimes cause a yellow precipitate of cuprous hydroxide. An alkaline solution of uric acid placed on a filter paper with a drop of silver nitrate reduces it to metallic silver with the production of a brown stain ; this is known as *Schiff's test*. The structural formula for uric acid is



As uric acid is a purine derivative it is related to the purine substances derived from nucleo protein and these substances will be

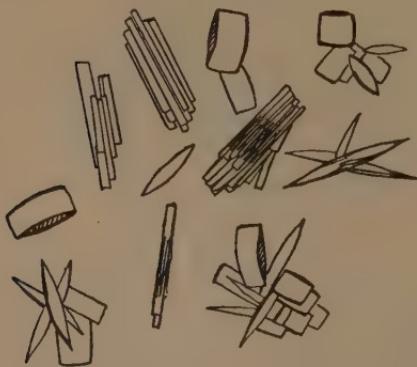


FIG. 84.—Crystals of Uric Acid  
( $\times 100$ ).



FIG. 85.—Crystals of Ammonium Urates ( $\times 100$ ).

discussed later (see p. 272). Being only slightly soluble it frequently precipitates from the urine. It precipitates from acid urine as uric acid or from alkaline urine as ammonium urate.

The yellow colour of normal urine is due to a pigment called *urochrome*. It is not known whether this term includes more than one substance, but a pyrrole derivative, possibly formed from chlorophyll, is responsible for part of the colour of the urine. Other substances which can form pigments are present, but they are either present in only small quantities, e.g. *haemato porphyrin* (see p. 241), or are in a colourless form e.g. *urobilinogen* which can be turned into the coloured substance *urobilin* (see p. 193).

*Urorosein* and *uroeryothrin* are two pigments which are sometimes present in urine.

**Hippuric Acid.** Another nitrogenous substance found in urine is hippuric acid. This can be crystallized from the urine of herbivorous animals by saturation with ammonium sulphate after acidifying it with sulphuric acid. It is formed by the linkage of benzoic acid with glycine.



The amount in human urine is less than that in the urine of herbivora ; hence it is not so easily obtained from human urine.

The student must remember that all sorts of waste products pass out in the urine. Some of these depend upon substances present in the diet or produced by bacterial action in the intestine. The concentration and amount of the urine varies greatly because of variable intake and changing activities in the body. Therefore we cannot give any one composition as that of "normal" urine but the following is given as the average output for twenty-four hours for an adult man doing a moderate amount of work and living in a temperate climate.

#### AVERAGE COMPOSITION OF HUMAN URINE

Total amount 1500 c.c. s.g. 1015—1025. It is usually acid in reaction to litmus (see p. 149). The total amount of solids is about 60 grams of which about 35 grams are organic and 25 grams inorganic. Urea accounts for about 90 per cent. of the total organic material.

TABLE XII  
COMPOSITION OF HUMAN URINE

| <i>Organic Constituents.</i>                            |                            |                      | <i>Inorganic Constituents.</i>   |                            |                      |
|---|----------------------------|----------------------|----------------------------------|----------------------------|----------------------|
|   | <i>Grams.<br/>per day.</i> | <i>Per<br/>cent.</i> |                                  | <i>Grams.<br/>per day.</i> | <i>Per<br/>cent.</i> |
| Urea . . . . .  | 30                         | 2·0                  | Sodium ions . . .                | 6·0                        | 0·4                  |
| Uric acid . . . .                                       | 0·75                       | 0·05                 | Potassium ions . . .             | 3·0                        | 0·2                  |
| Creatinine . . . .                                      | 1·0                        | 0·067                | Magnesium ions . . .             | 0·3                        | 0·02                 |
| Hippuric acid . . .                                     | 0·75                       | 0·05                 | Calcium ions . . .               | 0·2                        | 0·013                |
| Other organic substances (pigments, amino-acids, etc.). | 2·5                        | 0·167                | Ammonium ions . . .              | 0·75                       | 0·05                 |
| Total organic materials                                 | 35·00                      |                      | Chlorine ions . . .              | 9·1                        | 0·6                  |
|   |                            |                      | Phosphate ions . . .             | 2·5                        | 0·167                |
|   |                            |                      | Sulphate ions . . .              | 2·5                        | 0·167                |
|   |                            |                      | Other inorganic substances . . . | 0·2                        | 0·013                |
|   |                            |                      | Total inorganic substances       | 24·55                      |                      |
|   |                            |                      | Total solids                     | 59·55                      |                      |

The quantities of inorganic materials are expressed as the corresponding ions as that is the condition in which most of them will be present. On evaporation the inorganic material will be present mainly as sodium chloride.



FIG. 86.—Crystals of Calcium Oxalate ( $\times 100$ ).

FIG. 87.—Crystals of Ammonio-magnesium (Triple) Phosphate ( $\times 100$ ).

The inorganic constituents may be precipitated under different conditions. Oxalic acid is present in small quantities and under some conditions calcium oxalate crystals are formed.

(a) In *Acid Urine*, uric acid, as mentioned above, may crystallize : Calcium oxalate may be precipitated. Ammonium-magnesium phosphate and acid calcium phosphate are occasionally deposited.

(b) In *Alkaline Urine*. Ammonium urate may be precipitated. Calcium and magnesium phosphates are always precipitated when

normal urine is rendered alkaline or when the urine becomes ammoniacal by bacterial fermentation. The usual forms in which the phosphates are precipitated is that of ammonium-magnesium phosphate, " triple " phosphate, but calcium phosphate is sometimes found. Calcium carbonate is occasionally precipitated.

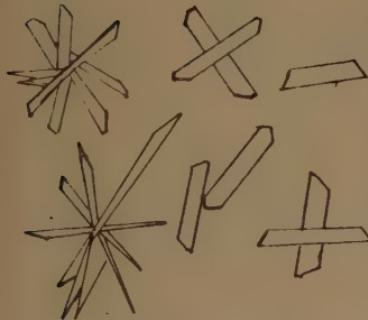


FIG. 88.—Crystals of Calcium (Stellar) Phosphate ( $\times 100$ ).

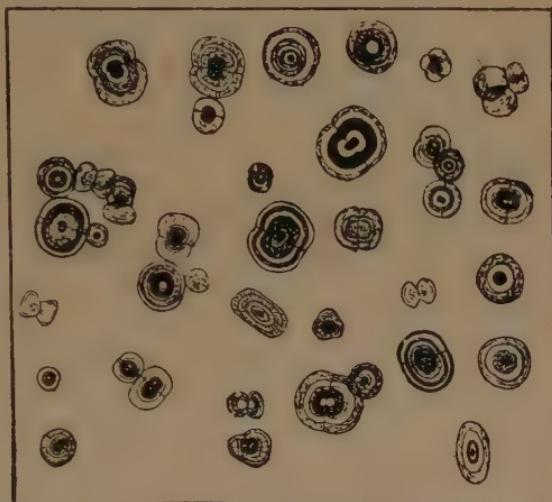


FIG. 89.—Crystals of Calcium Carbonate (from Human Urine) ( $\times 400$ ).

The intermediate stages between the food substances and the substances described in this chapter will be the chief study of the remaining chapters of this part on the chemical processes that occur in the body.

## CHAPTER X

### LAWS OF SOLUTION: HOMOGENEOUS SYSTEMS

The first stage in the utilization of food substances is their digestion, a process which renders them fit for absorption. During digestion the food which mainly consists of substances of high molecular weight and low diffusibility is converted into simple diffusible compounds. This definition indicates that we must have some knowledge of solution and diffusion before we can appreciate the process of digestion. At the same time so many of the problems that we must discuss require a knowledge of the chemical laws relating to solutions that a general description of these laws will help us in dealing with later problems. As the solvent which occurs in the body is water, the discussion will be of solutions in water.

The first general law is that substances in dilute solution behave as if they were gases occupying the same volume as the solution (van 't Hoff). Thus there is a tendency for the molecules to separate so that they pass from a region where they are more concentrated to one where they are less concentrated. This is known as *diffusion*.

If a solution is separated from some of the pure solvent by what is known as a semi-permeable membrane, that is one through which the solvent can pass, but not the dissolved substance (solute), the pure solvent will pass in to dilute the solution. This is known as *osmosis*.

**Osmosis** is related to the vapour pressure of the solution. Whenever a solute is dissolved in a solvent the molecules of the solute interfere with the freedom of movement of the molecules of the solvent. One effect of this is that evaporation of the solvent is less, or in other words the vapour pressure is decreased. If the vapour pressure of the solution is less than that of the solvent at the same temperature the pure solvent will evaporate and condense in the solution. The solvent must pass through a semi-permeable membrane because otherwise an equilibrium could not exist. Further, the decrease in vapour pressure is proportional to the molecular concentration of the solution so that if one draws the curve for vapour pressure of a solvent and a solution at different temperatures the solution gives a curve nearer the axis of zero pressure and

the distance between the two curves is proportional to the concentration of the solution. At the freezing point of water the vapour pressure curve shows a break so that the slope of the curve for the vapour pressure of ice is steeper than that of water near the freezing point. The result is that the vapour pressure curve of ice cuts the vapour pressure curve of the solution. This means that at some temperature below the freezing point of water, ice will separate from the solution. Because the decrease in vapour pressure of the solution is proportional to the molecular concentration it follows that the depression of the freezing point is proportional to the molecular concentration. This has been established experimentally and freezing point measurements are used to determine the molecular concentration of solutions.

On tracing the vapour pressure curve upwards the liquid boils when the vapour pressure becomes equal to that of the atmosphere. The vapour pressure curve for the solution being below that of the solvent a higher temperature is necessary to cause the solution to boil. The increase in temperature necessary to cause boiling is proportional to the concentration. Thus the rise of boiling point can be used to determine the molecular concentration of a solution. This method is not much used in Biology because proteins are coagulated by boiling, therefore the composition of the solution is altered.

If a solution is placed inside a semi-permeable membrane, the solvent passes through the membrane. If the solution is subjected to pressure solvent can be filtered through the membrane. When the osmosis and filtration balance each other a steady condition results. The pressure necessary to balance osmosis is known as the *osmotic pressure*, and it is that pressure which is produced when osmosis occurs into a closed space with rigid walls. This pressure is related to the vapour pressure so that osmotic pressure can be measured indirectly by the freezing point or boiling point methods.

The osmotic pressure of a solution is the pressure that the same substance would show if it were present in the form of gas occupying the same space as the solution, i.e. one molecular weight in grams would show a pressure of 760 mm. mercury when occupying 22.43 litres or if compressed to one litre the pressure would be 22.43 atmospheres.

The pressure produced by water movements due to changes in osmotic pressure is one of the two ways in which chemical energy may be converted into kinetic energy in living organisms.

The preceding statements require modification in that it has been assumed that the molecules exist in the solution as single particles. If two molecules are united together the osmotic pressure

will be only half of what it should be, or if the molecule breaks up into two or more particles the osmotic pressure will be greater than the volume calculated from the molecular weight.

In solution in water many substances give an osmotic pressure in excess of the calculated value. These substances have the additional property of facilitating the passage of the electric current. Those substances which increase the electrical conductivity of water, and which have an osmotic pressure higher than one would expect from their molecular weights, are called *electrolytes*, whilst those which do not increase the electrical conductivity of water are called *non-electrolytes*. The latter have either a normal osmotic or one lower than that corresponding to their molecular weight.

**Electrical Conductivity.** A rough but easy way of demonstrating the conduction of electricity is to connect an electric lamp in series with two conducting rods which are placed at a fixed distance from each other. If the apparatus is connected to the electric main and the two rods dipped into various solutions the brightness of the lamp will show the relative conductivities of the solutions. Thus distilled water and solutions of non-electrolytes such as sugars, urea, etc., do not allow sufficient current to pass for the lamp to light, but solutions of salts, acids, and bases give a greater or less illumination depending on the strength of solution and nature of the solute.

The property of conducting electricity depends on the dissociation of these substances into parts (ions), some of which carry positive electrical charges and the others negative charges; the degree of conductivity depending on the number of particles and their nature.

This dissociation into ions explains how all chlorides give the same reactions and how all dilute solutions of cupric salts have the same blue colour; further, the presence of electrolytes in living tissues is responsible for the electrical changes that take place during tissue activity and is related to the excitability of the tissues to electrical stimuli.

By passing an electrical current through a solution it is possible to separate the constituents into those carrying positive charge and those carrying a negative charge. When a constant current has been passed through a U tube containing sodium sulphate and indicators one limb will show an alkaline and the other an acid reaction. The positive current is carried from the positive pole to the negative by the positively charged sodium ion which with water gives an alkaline reaction whilst the negative charges are carried from the negative to positive pole by the negatively charged sulphate ion which with water gives an acid reaction.



The reaction of the separated ions with water leads to liberation of hydrogen at the negative and of oxygen at the positive pole.

It can be shown that the amount of electricity which passes through the solution depends on the number of positive and negative charges in the solution and also on the nature of the various ions in the solution. We can show a relation between the osmotic pressure and the electrical conductivity of a solution of a salt. The electrical conductivity is a function of the number of ions in the solution. The total number of ions which can be formed is limited by the total amount of salt in the solution.

Measurements of electrical conductivity show that as the concentration of the solution is decreased the electrical conductivity does not decrease so rapidly as does the concentration until a certain dilution is reached when the conductivity becomes proportional to the concentration. This condition shows that the salt is completely dissociated, but with the stronger solutions the salt is only partly dissociated. The molecular electrical conductivity is the observed conductivity divided by the molecular concentration.

The extent to which a salt is dissociated can be measured by the ratio of observed conductivity divided by the possible conductivity if the salt were completely dissociated at the same concentration. That is the molecular conductivity at a given concentration divided by the molecular conductivity at infinite dilution.

The extent of dissociation can also be measured by the ratio of observed osmotic pressure divided by possible osmotic pressure if the salt at the same concentration were completely dissociated into ions and each ion acted as a molecule in producing osmotic pressure. For a salt like sodium chloride the degree of dissociation is the same if measured by either method.

If the electrical conductivity of different electrolytes are compared for solutions in which the same number of ions are present it is seen that some electrolytes conduct better than others. This can be explained either by some ions carrying more than one electrical unit charge or that one ion travels faster than another. Both these conditions occur. The number of charges carried by an ion is related to the valency of the ion and the velocity of the ions is shown in the following table:—

TABLE XIII

## RELATIVE TRANSPORT VELOCITY OF VARIOUS IONS (OSWALD-LUTHER)

| Temperature | H <sup>+</sup> | <i>Cat-ions.</i> |                 | OH <sup>-</sup> | <i>An-ions.</i> |  |
|-------------|----------------|------------------|-----------------|-----------------|-----------------|--|
|             |                | K <sup>+</sup>   | Na <sup>+</sup> |                 | Cl <sup>-</sup> | $\frac{1}{2}$ SO <sub>4</sub> <sup>=</sup> |
| 18° C.      | 313            | 64.4             | 42.7            | 174             | 65.2            | 67   |
| 25° C.      | 340            | 73.8             | 50.5            | 196             | 75.2            | 77   |

Those ions that travel to the positive pole (anode) are called anions,

and those that travel to the negative pole (cathode) are called cations.

If we allow a strong solution to diffuse into a dilute solution the more rapidly moving ion will diffuse in front of the more slowly moving one so that the dilute solution acquires the electrical charge of the more rapidly diffusing ion, and the concentrated solution that of the more slowly moving ion. As the two ions have opposite charges they attract each other; separation will not take place, and the rate of diffusion of the salt is the average of the rate of diffusion of the two ions. Thus the slow ion is pulled forwards, and the fast ion is pulled back but the fast ion keeps in front of the slow one sufficiently to make the solutions have electrical charges. These are known as concentration cells because the electrical potential depends on the concentrations of the solutions. It has been proved that the electrical charge is dependent upon the following formula :—

$$E = \frac{u - v}{u + v} RT \log_e \frac{C_1}{C_2}$$

where  $E$ =electromotive force in volts,  $u$ =velocity of the positive ion,  $v$ =velocity of negative ion,  $RT$  has the usual significance and equals 0.0250 at 18° C. and  $C_1$  and  $C_2$  are the concentrations of the two salts with monovalent ions.

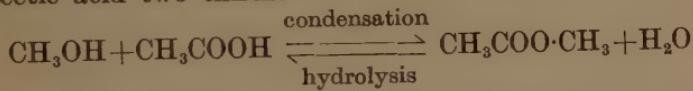
Salts which are only slightly dissociated in solution are called weak electrolytes in contrast with strong electrolytes which are highly dissociated into ions. Before we can understand the laws governing the electrolytic dissociation of weak electrolytes we must know something of the laws governing chemical reactions in solution; these laws are also of great importance in later chapters where we will discuss the chemical changes that take place in various organs of the body.

### Law of Mass Action

From the kinetic point of view we can visualize a reaction as taking place only when the reacting substances come into contact with each other. The probability of a moving particle coming into a given area will depend on the number of these moving particles in a given volume. That is, the probability of a chemical change taking place is dependent on the molecular concentration of the solution. Where the concentration of only one substance is involved the rate of reaction is proportional to the concentration of that substance, and the rate of chemical change decreases as the amount of that substance decreases by its decomposition, i.e.,  $\frac{dx}{dt} = -kC$ .  $\frac{dx}{dt}$  is the rate of increase of substance  $x$  at the time  $t$ , hence the minus sign.  $C$  is the concentration of the substance

at the time  $t$ , and  $k^1$  is a constant which can be determined for each reaction at a given temperature.

For example, if methyl alcohol and acetic acid are mixed in equal molecular proportions they unite to form a certain amount of methyl acetate and water. If on the other hand equal molecular proportions of methyl acetate and water are mixed, some methyl alcohol and acetic acid are set free. In each case if the mixture is left long enough the concentrations of methyl alcohol, acetic acid, methyl acetate and water reach the same values if the original mixture was either methyl alcohol and acetic acid or methyl acetate and water. The reaction proceeds according to the reversible equation and it is found that methyl alcohol and acetic acid represents one third of the molecular weight and methyl acetate and acetic acid two thirds.



Equilibrium is reached when the two rates of reaction are equal. The molecular concentrations can be represented by enclosing the chemical formulæ in brackets. At equilibrium the velocity:

$$-k_1 [\text{CH}_3\text{OH}] \cdot [\text{CH}_3\text{COOH}] = -k_2 [\text{CH}_3\text{COOCH}_3] [\text{H}_2\text{O}]$$

$$\text{or } \frac{[\text{CH}_3\text{OH}] \cdot [\text{CH}_3\text{COOH}]}{[\text{CH}_3\text{COOCH}_3] [\text{H}_2\text{O}]} = \frac{k_2}{k_1} = K$$

where  $K$  is called the equilibrium constant. When one constituent is present in excess so that its concentration does not change that term in the equation may be neglected. Therefore in dilute solution water is usually omitted from the equation.

This Law of Mass Action (Guldberg and Waage) states that the rate of reaction is proportional to the active masses of the reacting substances and that when equilibrium is established the reaction in both directions is equal. If two molecules of the same substance react its concentration must appear twice. Thus  $[\text{A}][\text{A}] = [\text{A}]^2$ .

Returning now to the electrolytes we find that weak electrolytes conform to the law of mass action although strong electrolytes do not follow the law in the simple form presented here. Thus the dissociation of a weak electrolyte is expressed by the equation

$$\frac{[\text{A}][\text{B}]}{[\text{C}]} = K \text{ or } [\text{A}][\text{B}] = K[\text{C}], \text{ where A and B are the two ions}$$

formed by dissociation and C the undissociated substance.

The characteristic feature of all acids is that they give rise to

<sup>1</sup> A constant is a mere number which makes the two sides of the equation balance. If the equation is correctly stated the constant will not vary throughout the reaction. But it will vary if the conditions of the experiment are altered, e.g. with change of temperature.

hydrogen ions and of all bases that they give rise to hydroxyl ions. Water can dissociate to a slight extent into hydrogen and hydroxyl ions. This dissociation is expressed by the law of mass action as  $[H^+] \times [OH^-] = K_w[H_2O]$ . The letters in square brackets represent the molecular concentrations of the corresponding ions, and as the concentration of water is not variable  $K_w[H_2O]$  can be abbreviated to  $K_w$ . This value  $K_w$  has been measured by several different methods and at 22° C. it has the value of  $1 \times 10^{-14}$ , which is equivalent to a concentration of a little less than one one hundred million millionth of a molecular solution.

As pure water dissociates into equal concentrations of hydrogen and hydroxyl ions a neutral solution is one in which the concentration of hydrogen ions is equal to the concentration of hydroxyl ions or  $[H^+] = [OH^-]$  thus

$$[H^+] \times [OH^-] = [H^+]^2 = K_w$$

$$\text{and } [H^+] = \sqrt{K_w}$$

Therefore the concentration of hydrogen ions in a neutral solution at 22° C. is  $\sqrt{1 \times 10^{-14}}$  or  $1 \times 10^{-7}$ , i.e. a little less than one ten millionth of a normal solution. These minute concentrations have, however, an extremely important relation to the living structures. Of the various methods that have been used to measure the concentrations of hydrogen and hydroxyl ions, at the present time, two are of importance in physiological investigations.

The first of these is an electrical method the principle of which is that a plate of a metal dipping into water gives off metallic ions. These metallic ions have a positive charge; therefore the plate is left with a negative charge. Various metals differ in the ease with which they give off ions: thus a voltaic cell can be formed by two plates dipping into a solution, the negative pole (usually zinc) being the one which most readily gives off positive ions. By adding a salt of the metal to the solution, ions of the metal pass less easily into solution: in fact they may even be deposited on the plate, thus causing a positive charge on the plate. The decrease of the electrical potential of such a plate is the basis for the measurement of the corresponding ions in the solution. It is fortunate that a platinum plate exposed to hydrogen gas behaves like a plate of hydrogen. Thus by keeping the pressure of hydrogen gas constant a "hydrogen" electrode can be used to measure the concentration of hydrogen ions in a solution.

In such measurements a second electrode is needed and the usual form is a "calomel" electrode. This has a constant potential, therefore if one calibrates one's instrument for known strengths of acid one can determine the concentration of hydrogen ions from

the electrical potential of the solution being measured. As the concentration of hydrogen ions multiplied by the concentration of hydroxyl ions is a constant the concentration of hydroxyl ions is known if the concentration of hydrogen ions is known

$$[\text{H}^+] \times [\text{OH}^-] = K_w \therefore [\text{OH}^-] = K_w / [\text{H}^+]$$

TABLE XIV

## ELECTROLYTIC DISSOCIATION OF PURE WATER (CLARK)

| Temperature. | Value of $K_w$ .       | Concentration of Hydrogen Ions, $[\text{H}^+]$ . |
|--------------|------------------------|--|
| 18° C.       | $0.74 \times 10^{-14}$ | $0.86 \times 10^{-7}$                            |
| 22° C.       | $1.00 \times 10^{-14}$ | $1.00 \times 10^{-7}$                            |
| 30° C.       | $1.88 \times 10^{-14}$ | $1.37 \times 10^{-7}$                            |
| 37° C.       | $3.13 \times 10^{-14}$ | $1.77 \times 10^{-7}$                            |

Owing to the mass law equation relating the concentrations of hydrogen and hydroxyl ions to the dissociation constant for water the reaction of solutions is frequently expressed in terms of hydrogen ions even when the solutions are decidedly alkaline, for hydrogen ions are still present though in the minority. The best way to express the reaction of a solution is in terms of normal solutions of hydrogen ions. The atomic weight of hydrogen is unity, therefore a normal solution contains one gram in a litre of solution.  $1/10$  N would contain  $0.1$  g. in a litre, etc.  $1/10$  can be written as  $1 \times 10^{-1}$ ,  $1/100$  or  $1/10^2$  as  $1 \times 10^{-2}$ , etc. Therefore a neutral solution containing a  $1 \times 10^{-7}$  normal solution of hydrogen ions is the same as  $1/10^7$  or  $1/10,000,000$  and it would contain one ten millionth of a gram of hydrogen ions per litre.

Recently a convention has grown up to use the Sørensen notation of PH. This is the logarithm of the divisor when the normality of the solution is expressed as a fraction in which the dividend is unity. In order to convert concentrations into this notation we must first of all express the concentrations in logarithmic notation and then arrange the fraction so that the dividend is unity.

$$\text{Thus } 2 \times 10^{-5} \text{ N} = \frac{2}{10^5} \text{ N.} \quad \text{Now } 2 = 10^{0.301}$$

$$\therefore \frac{2}{10^5} \text{ N} = \frac{1}{10^{5-0.301}} = \frac{1}{10^{4.699}}$$

Therefore the concentration of hydrogen ions represented by  $2 \times 10^{-5}$  N is equal to  $10^{-4.699}$  N or the concentration of hydrogen ions is  $\log[\text{H}^-] = -4.699$  or  $-\log[\text{H}] = 4.699$ . The symbol PH stands for  $-\log[\text{H}]$ .

In using this notation the student must remember that it represents a negative logarithm, therefore the greater the value of PH the less the acidity and vice versa,

In order to illustrate this method of expressing the values the following table is modified from Sørensen for solutions at 18°:—

TABLE XV  
HYDROGEN ION CONCENTRATIONS OF VARIOUS SOLUTIONS

| Solution.                          | Degree of<br>Dissociation,<br>per cent. | [H <sup>+</sup> ]       | —log[H <sup>+</sup> ] or PH |
|------------------------------------|---|-------------------------|-----------------------------|
| 0.1 N hydrochloric acid . . . . .  | 91                                      | 9.1 × 10 <sup>-2</sup>  | 1.04                        |
| 0.1 N acetic acid . . . . .        | 1.29                                    | 1.29 × 10 <sup>-3</sup> | 2.89                        |
| 0.1 N sodium hydroxide . . . . .   | 83                                      | 8.7 × 10 <sup>-14</sup> | 13.06                       |
| 0.1 N ammonium hydroxide . . . . . | 1.41                                    | 5.1 × 10 <sup>-12</sup> | 11.29                       |
| Neutral solution at 22° C. . . . . | —                                       | 1.0 × 10 <sup>-7</sup>  | 7.00                        |

As the value for the dissociation of water varies so greatly with the temperature the best way to represent the reaction is as the ratio [H<sup>+</sup>] [OH<sup>-</sup>] which is the same as [H<sup>+</sup>]<sup>2</sup>/K<sub>w</sub>.

The other method which is used for the measurement of hydrogen ions is by means of indicators. These are salts of weak acids or of weak bases.

A salt of a weak acid or a weak base is more highly ionized than the acid or base from which it is formed. Therefore if the free ion has a different colour from the unionized acid or base there will be a colour change when the acid or base is turned into a salt. It may be that the ionic change is accompanied by a tautomeric rearrangement of the molecule, but in all good indicators the tautomeric change is so rapid that only the ionic condition of the solution need be considered.

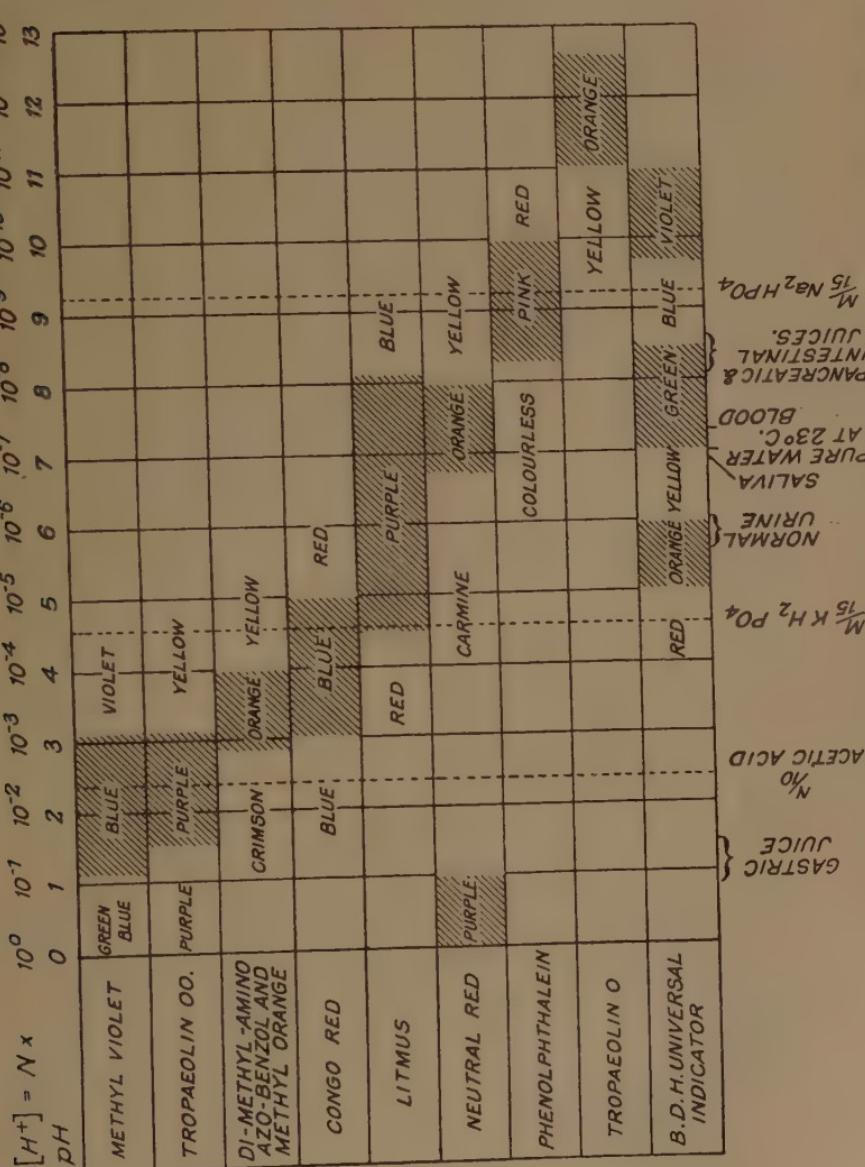
According to the law of mass action a weak electrolyte such as a weak acid will be dissociated according to the equation

[H<sup>+</sup>] × [X<sup>-</sup>] = K[HX] where X<sup>-</sup> and HX are the acidic ion and unionized acid respectively. If the total amount of acid remains the same any change in the concentration of hydrogen ions will cause a reciprocal change in the ion X<sup>-</sup>. The colour of X<sup>-</sup> will change over a certain range of concentrations of hydrogen ions, this being the range over which the indicator can be used to measure the hydrogen ion concentration.

The measurement is made by comparing the colour of the solution to which a definite quantity of indicator has been added with the colour of solutions of known hydrogen ion concentrations to which corresponding amounts of the same indicator have been added. The solution of known acidity which shows the same colour as the unknown solution is the measure of the hydrogen ion concentration of the unknown solution. In order to carry out this comparison it is necessary to prepare solutions of standard acidity. These mixtures are made so that they will neutralize small quantities of acid or of alkali without much change in reaction; they are therefore

called "stabilizer" or "buffer" solutions. The most frequently used ones are mixtures of primary and secondary phosphates.

Mixtures of solutions of phosphates will give a series of solutions



of different concentrations of hydrogen ions. Such solutions cover the range of hydrogen ion concentration of all physiological fluids except gastric juice and they are frequently used for standard solutions of known concentration of hydrogen ions. The con-

Fig. 90.—Diagram showing Range of Hydrogen Ion Concentrations over which certain Indicators change colour and the reaction of certain fluids.

centration of hydrogen ions can also be measured by the rate of hydrolysis of esters.

Methods for measuring other ions are of interest as the same principle is used in the so-called "non-polarizable" electrodes. The principle of these methods is that the potential at a metal surface depends on the concentration of metallic ions in the solution. Such an electrode is an electrode of the first order and is exemplified by the hydrogen electrode mentioned above. If, however, one uses a salt of the metal with low solubility the concentration of ions is related to the solubility according to the equation,  $C_A \times C_B = \text{constant}$  where  $C_A$  = concentration of metallic ions and  $C_B$  = concentration of acidic ions. The constant is known as the solubility product.

In the case of non-polarizable electrodes the aim is to have an electrode in which the potential does not change so that it can be used to measure the changes of potential at the surface with which it is placed in contact. A concentrated solution of a salt will maintain a constant potential at a metal plate with a corresponding ion. In the case of strong solutions these have a poisonous action on living tissues, so the strong solutions must be separated from the tissue by a solution of salts (Ringer's Solution), which does not injure the tissues. It is, however, more satisfactory to use salt with low solubility such as mercurous or silver chloride (see Table III, p. 39).

**Effect of Ions on Active Tissues.** For normal activity of tissues the correct concentrations of various ions must be present. In the absence of sufficient dissolved material of the right nature red blood corpuscles haemolyze. Even if the total molecular concentration is great enough the amounts and nature of the various ions is important for the activity of organs. The correct ratio of hydrogen to hydroxyl ions is of paramount importance and most cells can carry on their functions only when the reaction of the surrounding medium is near the neutral point.

The behaviour of the heart, when perfused by saline solutions, was investigated by Ringer (1882). He found that the heart of the frog would not continue to beat normally in a solution of pure sodium chloride. If calcium chloride was added to the perfusion fluid the heart stopped beating in systole. If potassium chloride was added to the sodium chloride solution the heart stopped beating in diastole. When both calcium and potassium chlorides were present the heart continued to beat for a long period of time. The two salts must be present in certain proportions, otherwise the activity of one or the other predominates. Such balanced action is interesting but its cause has not been explained.

A balanced solution of this sort is Ringer's Solution, which is used

for all experiments on excised living organs. The solution is kept slightly alkaline by the presence of some sodium bicarbonate or sodium phosphate. The concentrations which are used in making up Ringer's solution vary slightly, but the following are approximately correct:

|                    |   | <i>Percentage<br/>Frog.</i> | <i>Concentration for<br/>Mammal.</i> |
|--------------------|---|-----------------------------|--------------------------------------|
| Sodium Chloride    | : | 0·600                       | 0·900                                |
| Potassium Chloride | : | 0·014                       | 0·042                                |
| Calcium Chloride   | : | 0·012                       | 0·024                                |
| Sodium Bicarbonate | : | 0·020                       | 0·015                                |

Frequently a solution containing 0·1 per cent. glucose is used. This is called Ringer-Locke Solution.

This chapter shows us that in a solution diffusion, osmosis and osmotic pressure are all dependent on the differences in molecular concentration of the solutions. In the case of electrolytes the effective concentration is determined by the number of undissociated molecules and the oppositely charged ions formed by electrolytic dissociation.

The rate of chemical change is dependent on the concentrations of the various reacting substances in the solution and the product of these concentrations multiplied by a constant gives the rate of transformation. An equilibrium condition is reached when two opposing reactions are balanced and the equation for such an equilibrium state is applicable to the ionization of weak electrolytes.

Finally the concentration of ions can be measured by the electrical potential at certain surfaces.

## CHAPTER XI

### LAWS OF SOLUTION: HETEROGENEOUS SYSTEMS

The laws of solution in a homogeneous medium are not sufficient for a complete discussion of the reactions in the body. Cells are distinct from their surroundings and some of the food substances are not soluble in water.

Whenever more than one uniform medium is present two new factors are introduced. One of these is that there must be surfaces separating the two media; the other is that any substance in the mixture may be unequally distributed between the various parts thereof. The various homogeneous media are called phases.

#### PHENOMENA AT THE SURFACE OF A PHASE

One of the first steps in the process of digestion is the solution of such insoluble substances as starch. The rate of solution of a solid is proportional to the extent of its surface as the surface is that part which can be acted on by the solvent or any material which is rendering it soluble. Hence grinding a solid into small particles increases the rate of solution by increasing the area of contact between solid and solvent.

When a solid is dissolving the solvent near the surface of the solid takes up more and more of the solid until it becomes saturated. If the concentration near the surface is high the rate of solution is decreased. If mass movements do not occur the rate of action depends upon the rate of diffusion in the solvent. No more substance can dissolve until the saturated solution near the surface of the solid has been diluted by diffusion. Therefore movements such as those produced by stirring will hasten the rate of solution. In studying the process of digestion we shall find that grinding and stirring both occur in the alimentary canal.

**Surface Tension.** In the preceding chapter we mentioned semi-permeable membranes, i.e. ones which allow the solvent but not the solute to pass through. A membrane can cause in this way two distinct phases of different composition. We shall return to the subject of membranes later (see p. 161), but here we shall confine our attention to two phases without any membrane.

At the surface of a liquid in contact with another phase certain phenomena occur, foremost amongst which is a surface tension.

The proof that surface tension exists is as follows. Every surface tends to decrease in area. This can be shown by allowing a soap bubble to contract when it can be shown that the gas contained in the bubble is forced out through the tube on which the bubble has been blown. If a funnel is dipped into a soap solution the film that is formed across the mouth of the funnel, when it is lifted out of the solution, travels upwards against gravity to reach the narrower part of the funnel. Finally if a ring is bridged by a piece of thread and a soap film is formed across the ring the thread lies loosely in the film. If the soap film is broken on one side of the thread the film on the opposite side pulls the thread to that side. The cause of this surface tension is partly the unbalanced attraction of the molecules in the bulk of the liquid. The molecules near the surface are attracted by the molecules on their inner side but there are no similar molecules to attract them outside the liquid, hence they are pulled inwards to form an elastic skin. Another good example of this elastic surface skin is to dip a dry camel-hair brush into a beaker of water. The hairs of the dry brush and of the brush in water are separated from each other. On lifting the brush out of the water the surface tension of the water on the brush pulls all the hairs together to form a smooth surface.

Owing to this tendency for the surface to diminish small drops of a liquid suspended in another liquid become spherical (see Fig. 80) as a sphere has the smallest possible surface for a given volume. The contraction of the surface will produce a pressure greater inside the sphere than outside of it. This is indicated by the forcing of air out of a soap bubble.

The pressure on the concave side of a curved surface is always greater than that on the convex side according to the formula

$$P = \frac{T}{r_1} + \frac{T}{r_2} \text{ where } P = \text{the excess of pressure,}$$

$T$  = surface tension and  $r_1$  and  $r_2$  are the radii of curvature in two planes at right angles to each other and any uniformly curved surface can be described by two radii of curvature at right angles.

In the case of a sphere the two radii are equal, hence:—

$$\frac{T}{r_1} + \frac{T}{r_2} = 2 \frac{T}{r}.$$

In the case of a cylinder one radius is infinitely large so that  $\frac{T}{r_2} = 0$  ∴ the formula becomes  $P = \frac{T}{r_1}$ . Owing to the tendency for a surface to contract work can be done by the system and this is one way in which movement may be produced; the other means by which movement may be produced in the body is by passage of

liquid from one part to another owing to differences in vapour pressure (osmotic pressure).

Substances in solution frequently alter the surface tension; generally the surface tension is decreased by impurities. If a match-stick is placed on the surface of a vessel of clean water and a piece of camphor is stuck on one end of the stick the match will travel in the direction away from the end to which the camphor is attached. This is explained by the greater pull of the clean water contrasted with the lesser pull of the water in which the camphor is dissolving.

In the case of surface tension the force that is acting is the extent of surface pulling at right angles to the direction of action multiplied by surface tension. A decrease in surface tension will diminish the available force, i.e. the amount of work which can be performed by the system. A substance which decreases the surface tension will become more concentrated in the surface as the more concentrated the substance the greater is the decrease in surface tension. Some substances may become so concentrated at the surface that they precipitate there. Two illustrations may be given of this precipitating effect at the surface (Ramsden).

1. If a bubble is blown with a dilute solution of saponin and it is afterwards allowed to contract the precipitate of saponin wrinkles. The precipitate cannot contract smoothly as the surface of a soap bubble does.

2. If sublimed sulphur is sprinkled on the surface of clean water and a drop of soap solution is placed on the centre of the surface the sulphur is swept to the edges of the dish. The stronger pull of the pure water exceeds the weaker surface tension of the soap solution so that the latter is drawn over the whole surface. In pulling the soap solution over the surface the movement of the surface layer carries the sulphur with it. If instead of pure water the experiment is repeated with a dilute solution of protein (1/2,000 egg white) the protein becomes precipitated on the surface. On adding the drop of soap solution the surface cannot move freely, therefore the sulphur is held in the coagulated surface. The protein surface cracks and is drawn slightly away from the centre where the soap solution has been added. This concentration of substances at a surface of separation is a factor in adsorption (see p. 16).

Another means by which the surface tension may be altered is by altering the electrical charge on it. Similarly charged objects repel each other, therefore the greater the electrical charge the greater will be the repulsion between the particles. If molecules behave in the same way as larger charged objects it is clear that surface tension will be at its maximum when the surface is uncharged. Any increase in electrical charge on the surface will diminish the attraction between the molecules, thus decreasing the

surface tension. Compare this statement with the behaviour of the capillary electrometer.

**Differences in Concentration in Two Phases.** A substance distributed between two phases will not be equally distributed. A convenient way to demonstrate this is to shake in a test tube a mixture of ether and water containing some neutral red. The neutral red can be seen to pass into the ether when the mixture is alkaline and into the water when the mixture is acid. At certain ranges of acidity the neutral red will be present in both phases. This experiment shows the unequal distribution and that the distribution may be altered for instance by a change in acidity. It is true that the neutral red dissolves in the ether as a free base and in the water as a salt, but if we were estimating neutral red *qua* neutral red the concentrations would be reversed under the two conditions.

*Henry's Law* is that the distribution of a substance between two phases always shows a constant ratio. This is true provided the substance is always in the same molecular condition in the two phases. The solution of gases in water is a good example of such a constant ratio. The absorption coefficient is the ratio of the volume of a gas which is contained in a given volume of liquid to the volume of the same gas contained in the gas space. The absorption coefficient varies with the temperature and the presence of other substances in the solution.

The absorption coefficients in water for the gases of importance in physiology are shown in Table XVI.

TABLE XVI

| Temperature. | Oxygen. | Carbon dioxide. | Nitrogen. |
|--------------|---------|-----------------|-----------|
| 0            | 0.0489  | 1.713           | 0.0239    |
| 10           | 0.0380  | 1.194           | 0.0196    |
| 20           | 0.0310  | 0.878           | 0.0164    |
| 30           | 0.0262  | 0.665           | 0.0138    |
| 40           | 0.0231  | 0.530           | 0.0118    |

The absorption coefficient is defined as the amount of gas dissolved in 1 c.c. of liquid when the pressure of the gas above the liquid is equal to 760 mm. pressure.

If instead of water alkali were used the carbon dioxide would appear to depart from the above relationship. This apparent departure is due to the fact that the carbon dioxide forms a salt with alkali and the total amount of carbon dioxide obtainable from the solution is the sum of the dissolved carbon dioxide and that existing as a carbonate. The experiment described above with neutral red is an illustration of the same alteration in the condition of the substance in the solution.

**Electrical Charge at a Surface of Separation.** In the case of an electrolyte it may be that one ion is dissolved more readily in one phase whilst the other ion is dissolved more readily in a second phase. Although separation of the ions is prevented by the electrical attraction between the oppositely charged ions the phase boundary will be charged positively on one side and negatively on the other. This is sometimes called a Helmholtz double layer. There is an analogy between the diffusion potential in a concentration cell (p. 146), a membrane potential (p. 161) and this unequal solubility of ions in two phases.

The effects of a separation into phases are :—

- (1) There is a surface tension at the surface.
- (2) Some substances may be more concentrated at the surface than in the bulk of the phase.
- (3) If the surface is curved the pressure on the concave side will be greater than that on the convex side.
- (4) There will be an unequal distribution of substances in the various phases.
- (5) If a salt is present the ions of which dissolve differentially in the two phases an electrical potential will be established at the surface.

**Colloids.** When a phase is distributed in small particles throughout another phase the total amount of surface is greatly increased. Thus a sphere of oil with a radius of 1 cm. would have a volume of  $4/3\pi$  c.c.

If the volume of oil were broken up into spheres one micron ( $1/1,000$  mm.) in radius the volume of each would be  $4/3\pi(1/10,000)^3$  c.c., i.e. there would be  $(10,000)^3$  spheres. The surface of the large sphere would be  $4\pi = 12.56$  sq. cms., and each of the small spheres would have a surface of  $4\pi(1/10,000)^2$ . The total surface of the small spheres would be  $4\pi(1/10,000)^2 \times (10,000)^3 = 4\pi \times 10,000 = 125,600$  sq. cms. or 12.56 sq. metres.

Finer subdivision will cause a corresponding increase in total surface area. This great increase of surface has a considerable influence on the behaviour of these spheres. The same increase in surface occurs when a suspension of a solid is made instead of the emulsification of a liquid.

If the dispersion takes place to such an extent that the individual particles are not visible by means of the microscope the emulsion or suspension is said to be ultramicroscopic and we call the mixture of the two phases a colloidal solution. Although there is no sharp line at which we can distinguish colloidal solutions from suspensions or emulsions on the one hand and true solutions on the other the general characters of colloidal solutions are quite definite.

We speak of the phase that is suspended in the other phase as the

disperse phase, because it is dispersed into small particles, and we distinguish the liquid dispersions as emulsoids and the solid dispersions as suspensoids corresponding to emulsions and suspensions respectively.

The first noticeable characteristic of colloids is that they cannot diffuse through membranes such as parchment, parchment paper and collodion. It was this limitation of diffusion which caused Graham in 1861 to call them colloids, because one of the chief representative colloids studied by him was gelatin ( $\kappa\alpha\lambda\lambda\eta$ = glue).

That they are particulate is shown by the ultramicroscope. This consists of an application of the Tyndall phenomenon whereby invisible particles of dust become visible because of their diffraction haloes when viewed at right angles to a strong beam of light. The only difference is that in the ultramicroscope a microscope is placed at right angles to the strong beam of light so that the diffraction haloes of objects beyond the limit of the resolving power of the microscope become visible. In the "dark ground" method of using the microscope a similar result is obtained by having concentric rays of light which would not enter the microscope objective unless diffracted by particles in their path. The suspended particles are in movement (Brownian movement) and this movement is due to molecular forces comparable to the movements of molecules.

The permanence of a dispersion is dependent on two antagonistic forces, namely, the surface tension which tends to cause reduction of surface by the running together of the suspended particles and the electrical charge which by causing the particles to repel each other causes the dispersion to be maintained. By decreasing the surface tension to zero the two phases will mix and form a true solution. It is by reducing the surface tension of an oil by the addition of soap that permanent emulsions are formed. By decreasing the electrical charge to zero the dispersion is most easily precipitated and by increasing the electrical charge on the particles the dispersion is more permanent. These two influences are not independent. In discussing surface tension we pointed out that an electrical charge at a surface decreases the surface tension, thus these two factors are really both dependent on a common cause.

The electrical charge on most indifferent substances in contact with water is negative, therefore such suspended particles pass as a rule to the anode when a constant current is passed through the solution. If instead of suspended particles a mass of the material is arranged, such as a porous piece of earthenware, the water is moved relatively to the fixed indifferent material towards the cathode; this is known as electroendosmose.

The influence of the electrical charge on the disperse phase is such that the colloid is easily precipitated by oppositely charged

bodies and the precipitating action of neutral salts may depend on the electrical charges of the ions. One of the distinguishing features of suspensoids and emulsoids is that the former are more easily precipitated by salts than the latter.

Another way of describing colloidal solutions is to designate those which have an affinity for water and are consequently not easily precipitated as lyophile, whilst those which are easily precipitated as lyophobe. These two terms roughly correspond to emulsoid and suspensoid respectively without implying anything in reference to the liquid or solid state of the dispersed substance. In considering the behaviour of colloids we find that they can also be regarded as molecules of high molecular weight. Thus some colloids inside an osmometer may show a definite osmotic pressure. Further in the case of amphoteric colloids, such as solutions of protein, the protein can form salts with acids or with bases similar to the salts formed by amino-acids. Thus we find that a protein in an acid solution behaves as if it were a base, whilst in an alkaline solution it behaves as if it were an acid. Therefore the protein travels to the cathode in acid and to the anode in alkali.

By combining a colloid with an acid or base one finds that the osmotic pressure is raised, perhaps partly by increasing the dispersion of the colloid, but also because there are two ions instead of one. Although the inorganic ion may be able to pass through a membrane it is held back by the opposite electrical charge on the colloid and the osmotic pressure is the sum of the actions of the two. As the inorganic ion is able to pass through the membrane it produces a charge of the same sign as itself on the outer side of the membrane and the inner side of the membrane has the opposite sign. This electrical charge has been measured by Bayliss in the case of the sodium salt of Congo red. A similar charge must exist at the boundary of two immiscible solvents and each colloidal particle must have similar relations to the dispersing medium (p. 158).

In addition to the liquid state colloids may exist in a jelly condition. The former are called sols and the latter gels. Sometimes these can be reversed, as for example with gelatin where the gel condition is turned into a sol by warming. The change from a sol to a gel may depend on the relative volumes of the two phases. The phases of a colloid are influenced by the same forces that occur in true solutions. Thus a decrease in the vapour pressure of the disperse phase, which is equivalent to a rise of osmotic pressure, will cause some of the dispersing medium to pass into the disperse phase. Increase in volume of the disperse phase may cause it to be of greater volume than the dispersing medium, then the dispersing medium becomes the disperse phase.

Colloids are extremely unstable and the suspensoids are much less stable than emulsoids. Sometimes an emulsoid colloid protects a suspensoid from precipitation.

The protective action of emulsoid colloids in preventing the precipitation of suspensoid colloids by salts is generally measured in relation to the precipitation of a gold sol. Hence it is spoken of as the "gold" value.

**Adsorption.** Owing to the great increase in surface when one phase becomes dispersed in another phase, the effects of the surface tension become of great importance. Owing to the small radii of curvature the pressure, inside the disperse phase, may be of considerable value. The condensation on the surface of substances which decrease the surface tension may lead to considerable differences in composition, as for example the removal of pigments from a solution by animal charcoal.

These surface condensation effects are spoken of as *adsorption*, which is expressed by the formula (Freundlich) :—

$$\frac{x}{m} = ac^{\frac{1}{n}}$$

where  $x$  = amount adsorbed,  $m$  = mass of adsorbent (= surface),  $c$  = concentration in the solution when equilibrium is established, and  $a$  and  $\frac{1}{n}$  are constants,  $\frac{1}{n}$  being usually between 0.2 and 0.5.

The condensation of substances on a solid surface may not be entirely due to decrease in surface tension. Matthews ascribes the general effect to adhesion. We cannot say what causes the adhesion but we do know that the substance adsorbed does accumulate on the surface.

**Membrane Equilibrium.** Separation of phases by a semi-permeable membrane produces some of the effects described in this chapter. A colloidal solution consisting of the salt of a colloidal ion with an inorganic ion will cause an electrical charge across the membrane. The sodium salt of congo red placed inside a parchment paper membrane cannot diffuse through the membrane because the latter is impermeable to the congo red. The sodium ion could however pass through but it is held back by the opposite electrostatic charge on the congo red anion. Therefore the outside of the membrane is positively charged and the inside is negatively charged (see p. 158).

Another result of this membrane separation is that an inorganic salt such as sodium chloride with an anion common to it and to the colloid is distributed unequally between the two solutions. According to thermodynamical considerations, at equilibrium, the product of the concentrations of ions on the two sides must be equal.

Thus  $[Na_1^+] \times [Cl_1^-] = [Na_2^+] \times [Cl_2^-]$  where  $[Na_1^+]$  and  $[Cl_1^-]$  are the concentrations outside the membrane and  $[Na_2^+]$  and  $[Cl_2^-]$  are the concentrations inside.

As the concentration of sodium ions inside is greater than outside because of the sodium ions from the congo red salt, the concentration of chlorine ions inside must be less than that outside.

This unequal distribution across a membrane may be of importance in reference to the relation of cells to their surrounding media.

*Cells and the Phase Rule.* Although cells cannot be regarded as homogeneous solutions the relation of a cell to its surrounding medium can be regarded as an application of the phase rule. The cells contain colloids but the dispersing medium in the cell can be regarded as the solution in equilibrium with the solution outside the cell. The same laws which are applicable to the two phases apply even when one phase is separated into such small particles as those of colloidal solutions. Owing to the small mass and relatively large surface of the colloidal particles surface tension effects and electrical charges have a great influence on the behaviour of the disperse phase. The instability of colloidal solutions may have a great influence on the lability of protoplasm and may thus be of extreme importance in living cells. In addition to the cell surface and the surfaces of colloidal particles there are probably other surfaces of separation in cells which may influence their physiological activities.

## CHAPTER XII

### DIGESTION IN THE MOUTH: ENZYMES

Digestion commences with the entry of food into the mouth. Previous preparation by manufacturing processes and by cooking may have a considerable influence on the ease with which food is digested. The aim of digestion is to convert insoluble or non-diffusible colloidal substances into soluble diffusible substances. An important aid to the process of solution is the division of the food into minute particles because in that way the surface for the action of the solvent is increased. The process of grinding is accomplished by the teeth. The tongue, cheeks and jaws all co-operate to triturate the food until it is in a fine state of subdivision. Whilst the food is being masticated it is mixed with the secretions from the three pairs of salivary glands and the glands of the mouth.

We find that there are two types of secreting cells, one of which furnishes a thin watery secretion and the other a thick slimy secretion. Sometimes these are found in separate glands and sometimes in the same gland. Fig. 91 shows the two types of secreting cells in the same gland.

*Serous and Mucous Glands.* The cells which secrete the thin watery secretion form serous glands and those which secrete the slimy secretion constitute mucous glands. The serous secreting gland possesses cells which are usually more opaque than those of the mucus-secreting gland. The mucous gland alveoli contain a few cells which appear like serous secreting cells. These are arranged in a crescentic margin to the end of the tubule: hence they are called crescents. The slimy secretion due to mucin is merely for the process of lubrication. We find mucus-secreting cells throughout the alimentary canal, but especially at the two extremities where the food is less liquid and therefore requires more lubrication. In some species, for instance the dog, the saliva functions only as a lubricant.

#### Saliva.

In some animals the saliva has a chemical action on the food. If a solution of starch is mixed with saliva (of man for instance) the starch which is viscous and opaque becomes thin and limpid. On adding iodine solution to the mixture the blue colour due to starch may still be seen. As this solution is clear the starch paste has been transformed into soluble starch. If the mixture is

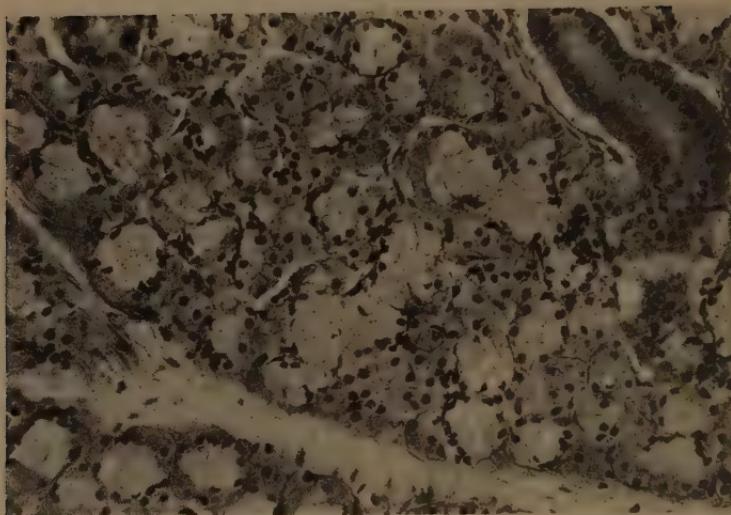


FIG. 91.—Photomicrograph of Mixed Salivary Gland ( $\times 100$ ).  
A duct is seen at the right upper corner. Mucus-secreting (transparent) alveoli are seen with crescents of Gianuzzi. Some serous (opaque) alveoli can be seen between the mucous alveoli.

left for a short time at body temperature it will be found that the colour given with iodine becomes red instead of blue. The starch has been converted into erythrodextrin. Later on no colour save the yellow colour of the iodine will be seen when iodine is added to the mixture. Any dextrin still present must now be in the form of achroodextrin. If some of the solution is now boiled with Fehling's Solution a reducing sugar can be shown to be present and by the phenyl-hydrazine test it can be proved that this sugar is maltose. Thus we see that the starch is hydrolyzed through the stages of the polysaccharides, erythro- and achroodextrins, to form the disaccharide maltose. It is probable that the process consists of splitting off successive molecules of maltose leaving a smaller and smaller molecule at each stage. There are really a long series of intermediate dextrans but we need recognize only the two which are differentiated by their reaction with iodine. The agent which produces this effect is named *ptyalin*.

TABLE XVII  
COMPOSITION OF SALIVA (C. L. EVANS)

|   |                                |
|---|--------------------------------|
| Water . . . . .                         | 99.365                         |
| Mucin . . . . .                         | 0.275                          |
| Other organic solids . . . . .          | 0.135                          |
| Chlorine . . . . .                      | 0.052                          |
| P <sub>2</sub> O <sub>5</sub> . . . . . | 0.067                          |
| Ash insoluble in water . . . . .        | 0.026                          |
| Other inorganic matter . . . . .        | 0.080                          |
|   | Total organic matter = 0.41    |
|   | Total inorganic matter = 0.225 |

From the analysis we see that inorganic salts are also present. Some calcium bicarbonate is found in fresh saliva. On standing, carbon dioxide is given off and calcium carbonate is precipitated, forming one of the constituents of the tartar deposited on the teeth. Another substance which can be shown to be present is a thiocyanate. This can be recognized by the addition of ferric chloride. As the amount of thiocyanate is small one does not obtain the red colour usually seen with thiocyanates, but a reddish or flesh colour may be all that is visible.

### Catalysts

In order to convert starch into sugar it is necessary to boil it for some time with moderately strong acid; the end product is glucose. A substance which acts in this way is called a catalyst as it does not enter into the reaction and can be obtained unchanged at the end of the process. The characteristic of a catalyst is that it is not used up, hence it can produce an unlimited amount of change if given sufficient time. If the active agent united with the substrate so that the resultant contained some of the active agent the amount of material changed would depend upon the amount of active material added to the mixture. It is usually assumed that the reaction which is hastened by the catalyst is proceeding but extremely slowly. It may be, however, that the catalyst decreases the resistance to chemical change, so that a reaction which is at a standstill may start. Bayliss has suggested the analogy of a catalyst to a weight on an inclined plane. The weight may be stationary or sliding slowly. A drop of oil may cause the stationary weight to slide and it will increase the rate of the moving weight. The oil represents the catalyst. The chemical potential which causes the reaction corresponds to the sloping surface.

In the case of saliva we saw that the reaction was brought about in the absence of a strong acid and at body temperature, but the action is still that of a catalyst. We can show that the ptyalin is not destroyed during the action. As the substances which accelerate chemical change in the body have certain peculiarities we classify them as a special group of catalysts, namely enzymes. We shall now study the enzymes by investigating the effect of various conditions upon their activity.

### Enzymes

The factors to be discussed are :—

- I. The effect of change of temperature on the rate of enzyme activity.
- II. The effect of acidity and of alkalinity on their activity.
- III. The effect of concentration of substrate on the rate of action.

IV. The effect of concentration of the enzyme on the rate of action.  
The last two must be considered in their relation to each other.

#### I. THE EFFECT OF TEMPERATURE ON THE RATE OF ENZYME ACTION

Starting at a low temperature it is found that the enzyme activity increases with rise of temperature to a maximum rate. With higher temperatures the rate falls off rapidly to zero. The increase in activity with rise of temperature is shown by most chemical reactions. The increase for each rise of ten degrees Centigrade is such that the rate at the higher is usually double or treble what it was at the lower temperature. This is an example of a geometrical progression and it may be expressed by the formula :—

$$\frac{\text{Rate at higher temperature}}{\text{Rate at lower temperature}} = K \frac{t_2 - t_1}{10}$$

where K is a constant called the temperature coefficient and  $t_2$  and  $t_1$  are the two temperatures at which the rate of reaction is measured.

When the difference of temperature is ten degrees the ratio is called the temperature coefficient of the reaction. Many physiological processes show a similar relation to the temperatures at which they are carried out. That is they increase in geometrical progression with rise of temperature. The fall in activity at higher temperatures is due to the destruction of the enzyme. If a solution of ptyalin is boiled it will no longer hydrolyze starch to maltose. At lower temperatures the enzyme is destroyed and the rate of destruction depends on the temperature.

In order to show the action of ptyalin on starch the enzyme must be allowed to act for a definite period of time. If the rate of reaction continues to rise with rising temperature not only will the rate of hydrolysis of starch increase but the rate of destruction will also increase. When the rate of destruction is sufficiently rapid the enzyme will be destroyed before an appreciable amount of sugar has been formed. Under these conditions the amount of sugar formed will be less than when the enzyme is not destroyed even if the rate of hydrolysis is somewhat slower at the lower temperature.

The balance between increased rate of enzyme activity and increased rate of enzyme destruction results in a range of temperatures at which the enzyme activity is at a maximum. This is called the "optimum" temperature for the enzyme.

#### II. THE EFFECT OF ACIDITY OR ALKALINITY ON THE RATE OF ENZYME ACTIVITY

Some enzymes show a very intimate relation between the reaction of the medium and the rate of chemical change produced by them.

Most enzymes are active near the neutral point and they are all destroyed by marked acidity or alkalinity. A few enzymes are active only when the solution is definitely acid whilst others are active only in alkaline solutions. They are usually more easily destroyed by acidity or alkalinity on the opposite side of the neutral point from that in which their activity is greatest. Within the range of hydrogen ion concentration at which they do act the concentration of hydrogen ions has a marked influence on their activity. The effect of reaction may be explained by assuming that the amount of enzyme which is active depends on the hydrogen ion concentration. This possibility will be discussed in relation to the effect of concentration of enzyme on the rate of enzyme action.

### III AND IV. THE EFFECT OF CONCENTRATION OF ENZYME AND OF SUBSTRATE ON THE RATE OF ENZYME ACTION

The clearest way to demonstrate the effects of the concentrations of enzyme and substrate is to keep one of these present in a minimal quantity. If one uses a small quantity of enzyme and a large amount of substrate it is found that the rate of reaction is proportional to the small quantity of enzyme added. If one uses a large quantity of enzyme and a small quantity of substrate the rate of reaction is now proportional to the amount of substrate added. This can be compared to men carrying bricks from a pile of bricks. If the men are few in number the number of bricks carried will depend on the number of men working, but with many men working the number of bricks carried will depend upon the size of the pile, because with a small pile the men will have to wait in a queue for each to get their quota of bricks.

This is expressed by the law of mass action (see p. 146). The rate of reaction is proportional to the concentrations of the reacting substances. If the enzyme is looked upon as one of the reacting substances the formula can be written—

$$dx/dt = -kC_e \cdot C_x$$

where  $dx/dt$  represents the amount of substance  $x$  formed in time  $t$ ,  $k$  is the numerical figure of proportionality,  $C_e$  and  $C_x$  are the concentrations of enzyme and substrate respectively. The minus sign indicates that the concentration of the substrate is decreasing during the reaction.

The effect of acidity or alkalinity in altering the rate of reaction can be explained by assuming that an active form of the enzyme is produced from an inactive form. In this case the rate of reaction would not depend on the total amount of enzyme added but only on the amount of active enzyme formed from the added enzyme.

If we were to compare the activity of an enzyme with an ampho-

teric substance such as *p*-amino-benzoic acid we could show that the rate of reaction would be related to the acidity according to whether the active portion were the neutral unionized *p*-amino-benzoic acid; *p*-amino-benzoic acid acting as a base, for example combined with hydrochloric acid, or *p*-amino-benzoic acid acting as an acid, for example as the sodium salt by reaction with sodium hydroxide. For a given quantity of *p*-amino-benzoic acid the concentrations of the three forms, mentioned above, are given in Table XVII, showing that the respective maximum activities would be at different concentrations of hydrogen ions.

TABLE XVIII

DISSOCIATION OF *p*-AMINO BENZOIC ACID AT DIFFERENT CONCENTRATIONS OF HYDROGEN IONS

| Concentration of hydrogen ions. | As Positive ion. | Percentage of <i>p</i> -amino benzoic acid As Unionized acid. | As Negative ion. |
|---------------------------------|------------------|---|------------------|
| $10^{-1}$                       | 95.0             | 5.0   | —                |
| $10^{-2}$                       | 70.0             | 30.0  | —                |
| $10^{-3}$                       | 10.6             | 88.7  | 0.7              |
| $10^{-4}$                       | 2.2              | 91.4  | 6.4              |
| $10^{-5}$                       | —                | 60.0  | 40.0             |
| $10^{-6}$                       | —                | 13.0  | 87.0             |
| $10^{-7}$                       | —                | 1.0   | 99.0             |

The maximum of the unionized acid would be about  $[H^+] = 10^{-4}$ ; the positive ion is at a maximum about  $[H^+] = 10^{-1}$  and the negative ion at a maximum about  $[H^+] = 10^{-7}$ . As an enzyme does not form a permanent compound or enter into the final products of the reaction it cannot affect the equilibrium condition, namely

$$\frac{C_A \times C_B}{C_C \times C_D} = \frac{k''}{k'} = K.$$

Therefore it must affect both velocity constants  $k''$  and  $k'$  to the same extent. In that case an enzyme will affect both synthesis and decomposition to the same degree. In most cases the equilibrium condition is so close to a complete reaction that increased rate of synthesis is not so easy to demonstrate as the increase in decomposition.

**Nature of Changes accelerated by Enzymes.** *Nomenclature.* The chemical changes accelerated by enzymes are of two main classes. First there are the reactions involving a loss or gain of one or more molecules of water. The usual change is to add one molecule of water, the compound breaking down into two simpler bodies. This is called hydrolysis and these are the group of hydrolytic enzymes. We can distinguish the kind of material hydrolyzed by using the terms amyloclastic, lipoclastic or proteoclastic for starch splitting, fat splitting and protein splitting respectively.

The names of the individual enzymes are formed by the suffix *-ase* added to the root of the word denoting the substance acted upon except in the case of certain well-established terms for which we retain the names originally given to these enzymes.

The second group of reactions are those involving a change in oxygen. These differ from the former in that there is usually an appreciable energy change associated with the chemical change, whilst in hydrolytic reactions the energy loss is at a minimum.

The hydrolytic enzymes will be discussed under digestion and the oxidizing enzymes under respiration.

There are other types of reaction such as deamination or the removal of amine groups, but these may be due either to hydrolysis, oxidation or both.

**The Mode of Action of Enzymes.** There are two ways in which enzymes may accelerate the rate of reaction. The first is by the formation of an intermediate compound between the enzyme and substrate. This compound breaks down into the enzyme and the products of its action. The rate of combination and decomposition is such that they occur in less time than the decomposition of the original substance itself. The best known example of this form of catalysis is the oxidation of  $\text{SO}_2$  to  $\text{SO}_3$  by oxides of nitrogen.

The second way in which an enzyme may accelerate the rate of reaction is that the enzyme being a colloid the reacting substances (substrate and water) condense on the surface of the colloidal particles, thus increasing the effective concentrations. For example, spongy platinum condenses hydrogen to such an extent that combination with oxygen becomes sufficiently rapid to make the platinum red hot.

It has been determined that one volume of platinum can adsorb more than 1,000 volumes of hydrogen, which is equivalent to increasing the concentration 1,000 times. If both substances are concentrated to that extent the rate of reaction will be increased  $1,000 \times 1,000$  or one million times. In other words an amount of reaction which would take eleven days without the catalyst could be completed in one second.

**Specific Nature of Enzymes.** In attempting to decide which of these two modes is the more probable explanation of enzyme action some stress must be laid on the specific nature of enzyme action.

A catalyst such as hydrochloric acid can hydrolyze all the carbohydrates to the stage of monosaccharides, but it requires separate enzymes for most of the carbohydrates.

This specific relationship to the substrate has given rise to two similes, namely that an enzyme must fit its substrate like a key fits a lock (Fischer), or as a hand fits a glove (Armstrong). Such

TABLE XIX  
HYDROLYTIC ENZYMES

| <i>Enzyme.</i>                    | <i>Substrates.</i>             | <i>Products of Hydrolysis.</i>             |
|-----------------------------------|--------------------------------|--|
| Ptyalin (salivary amylase)        | Starch, dextrin or<br>glycogen | Maltose                                    |
| Amylopsin (pancreatic<br>amylase) |                                |  |
| Maltase . . . . .                 | Matlose                        | Glucose                                    |
| Lactase . . . . .                 | Lactose                        | Glucose and galactose                      |
| Sucrase . . . . .                 | Sucrose                        | Glucose and fructose                       |
| Lipase . . . . .                  | Fats                           | Glycerol and fatty acids                   |
| Pepsin . . . . .                  | Proteins                       | Peptides                                   |
| Trypsin . . . . .                 | Proteins                       | { Peptones, polypeptides<br>and aminoacids |
| Erepsin . . . . .                 | Proteoses and pep-<br>tones    | Amino acids and polypep-<br>tides          |

a specific relation is more like a chemical reaction, but the problem is not yet settled. Another interesting point about the specific relations of enzyme to substrate is that if the enzyme combines with one form of molecule more than another one of the products of reaction may combine with the enzyme and interfere with the rate of reaction.

Thus we see that enzymes can accelerate chemical changes by acting on specific substances, that the enzymes are destroyed by boiling and are affected by the conditions under which they are acting, namely temperature, reaction and concentration. These effects will be applied to the process of digestion.

#### METHODS USED FOR TESTING FOR THE ACTION OF ENZYMES

##### A. Hydrolytic Enzymes

1. *Amyloclastic Enzymes.* The action of enzymes which hydrolyze starch, glycogen or dextrin can be demonstrated in two ways, namely by the disappearance of the characteristic colour given by the polysaccharide with iodine and by the formation of reducing sugar from the non-reducing polysaccharide. The former can be applied quantitatively by noting the time necessary for the replacement of the blue colour with starch by that of the red colour given by dextrin, or the time necessary for the polysaccharides to be converted into substances which no longer give a colour with iodine. The latter method is to measure the amount of reducing sugar formed after a definite period of action of the enzyme.

2. *Sucroclastic Enzymes.* Hydrolysis of sucrose can be demonstrated by the formation of reducing sugar and a quantitative estimation made of the same. Hydrolysis of maltose and of lactose is less easily shown. The simplest method is to use Barfoed's reagent, which shows the conversion of disaccharides into mono-

saccharides. Otherwise one must make careful quantitative estimations either of the reducing power of the solutions before and after the enzyme action or of the change in rotation of polarized light caused by the activity of the enzyme.

3. *Proteolytic Enzymes.* Three methods can be employed to measure the rate of action of proteolytic enzymes.

The first is to measure the rate of solution of an insoluble protein. The rate of solution may be determined; by weighing the protein before and after a definite time of action; by the colour of the solution due to the setting free of a dye by the solution of the protein; or by a solution becoming transparent when a suspension of insoluble protein becomes dissolved. For comparative measurements the amount of surface should be the same, hence the insoluble protein must be in as fine a state of subdivision as possible.

The second method is to precipitate the protein by heat coagulation, by trichloroacetic acid, by tannic acid or by some other precipitant. The amount of nitrogen left in the filtrate is determined by Kjeldahl's method; as the protein is digested the amount of nitrogen not precipitated by the reagents will increase.

The third method of measuring the proteolytic activity of an enzyme is to make use of the condensation of formaldehyde with NH<sub>2</sub> groups. The solution is neutralized to phenolphthalein and neutral formaldehyde is added: the formaldehyde combines with the NH<sub>2</sub> groups. Thus the neutral peptides are changed to acid substances (owing to masking of the basic NH<sub>2</sub> group) and sufficient alkali must be added to neutralize these acids. Hydrolysis of proteins leads to an increase in NH<sub>2</sub> groups, hence the amount of alkali used is a measure of the degree of splitting of the protein.

4. *Fat-splitting Enzymes.* These are estimated by the amount of fatty acid set free during hydrolysis. Titration with a solution of alkali in the presence of phenolphthalein is all that is required.

## B. Oxidizing Enzymes

(1) *Peroxidases.* These are usually demonstrated by the production of colour when such aromatic substances as tincture of guaiacum or a solution of benzidine are treated with the enzyme and hydrogen peroxide.

(2) *Oxygenase.* If the enzyme produces colour with the above aromatic substances without the addition of hydrogen peroxide then an oxygenase is present. This really means that some substance is present which can form a peroxide from molecular oxygen. It is possible that this is a catechol-like substance.

(3). *Catalase.* Catalase is of no special importance in Biology, since the addition of hydrogen peroxide to all colloids results in the evolution of oxygen.

Enzymes differ from such catalysts as hydrochloric acid or sodium hydroxide in two ways :—

1. They are destroyed by boiling.
2. They are specific in action. Hydrochloric acid or sodium hydroxide will act on all the substances in Table XVI and produce the simplest possible bodies, whilst the enzymes act only on special substances and the products of their activity may be hydrolysis only to an intermediate stage.

**Ptyalin.** The enzyme of the saliva acts on cooked starch, glycogen and dextrin converting them into maltose. It is without action on disaccharides and will attack uncooked starch slowly if at all. It exhibits its greatest activity in very faintly acid solution near the neutral point. It is rapidly destroyed before the temperature reaches 60° C.

**Secretion of Saliva.** The secretion of saliva is controlled through the nervous system in response to the stimulation of various sense organs. The sight, smell or taste of food, and even the thought of food, will cause a secretion of saliva. This secretion is abolished if the nerves to the salivary glands are cut. This process of reflex secretion must be studied after we know something about the central nervous system, but as we shall meet other examples of such secretion, it is necessary to point out that such a reflex requires a receiving (receptor) organ, a path to the nervous system, the nervous system, a path from the nervous system and the active (effector) organ.

Accompanying the process of secretion are histological changes in the glands. During the resting intervals the cells of the glands become filled with granules and during activity the granules are reduced in number so that there may be only a few left close to the lumen of the duct (see Fig. 100). In the dog the disappearance of the granules is accompanied by a decrease in the nitrogen of the gland (Anrep). The granules are believed to be the material which is transformed into the secretion. If we attempt to obtain the enzymes from the glands it is usual to make extracts in water or glycerol and the extracts can be purified by methods of precipitation such as precipitation by alcohol. Sometimes the enzymes are carried down by insoluble substances such as calcium phosphate, precipitated by the addition of calcium salts and soluble phosphates.

When extracts are made of the fresh glands they are found to be without action on starch but the addition of a trace of acid to these extracts makes them active. Therefore it is said that the gland contains ptyalinogen which is converted into ptyalin as the granules are converted into the secretion. The suffix *-ogen* always indicates a substance which is converted into another substance, the name of which forms the root of the word.

The process of digestion in the mouth consists of a secretion of saliva brought about by a nervous impulse in response to stimulation of certain sense organs. In the case of all animals the secretion is accompanied by conversion of mucinogen into mucin, and in those animals which have a salivary amylase there is a conversion of ptyalinogen into ptyalin.

## CHAPTER XIII

### DIGESTION IN THE STOMACH

The first stage of digestion and the manner in which the chemical changes of digestion are brought about have been described in the preceding chapter.

The next stage is the passage of food into the stomach and the chemical changes which occur in the stomach.

**Swallowing.** After the food has been lubricated and mixed with saliva it is swallowed. This process is divided into three stages. The first stage is the passage of the food from the mouth. The second stage is its passage through the pharynx where the alimentary canal and respiratory passages share a common tube. The third stage is its passage down the oesophagus.

The first two stages are rapid so as to interfere as little as possible with respiration, whilst the third stage is slower and introduces us to the processes by which muscular tubes propel their contents. The first stage consists of the food being rolled into a mass called a bolus, which is well lubricated by the mucin of the saliva. The tip of the tongue is placed against the hard palate and then the rest of the tongue is pressed upwards. The bolus is squeezed between the inclined plane of the tongue and the hard palate so that it is shot backwards very much in the same way that a slippery orange pip can be projected by squeezing it between the thumb and forefinger.

As soon as the bolus touches the pharynx there is a reflex contraction of the constrictors of the pharynx. This causes pressure on the slippery bolus so that it is squeezed out of the pharynx. The direction in which it is squeezed is governed by the fact that the only available opening is downwards into the oesophagus. The bolus cannot pass back into the mouth because the tongue is pressed against the hard palate. It cannot pass upwards towards the nose because the soft palate is lifted so as to come into contact with the posterior wall of the pharynx.

In its passage downwards the bolus is prevented from entering the larynx because it is closed in the following manner.

During swallowing the larynx is lifted and this can be observed by inspection or by feeling the larynx during swallowing. In this

way the opening of the larynx can be drawn together by its sphincter muscles, the aryteno-epiglottidei.

Once the bolus reaches the oesophagus it travels more slowly and the nature of its propulsion requires further consideration.

#### THE METHODS THAT CAN BE USED TO STUDY THE ACTIVITY OF HOLLOW MUSCULAR ORGANS

(a) Inspection. The parts may be exposed and their movements watched.

(b) Examination when isolated. The portion to be studied may be removed, suspended in warm oxygenated Ringer Solution, and records made of its movements by attaching threads running to levers to various parts of it.

(c) A distensible bag may be placed inside it and the bag con-

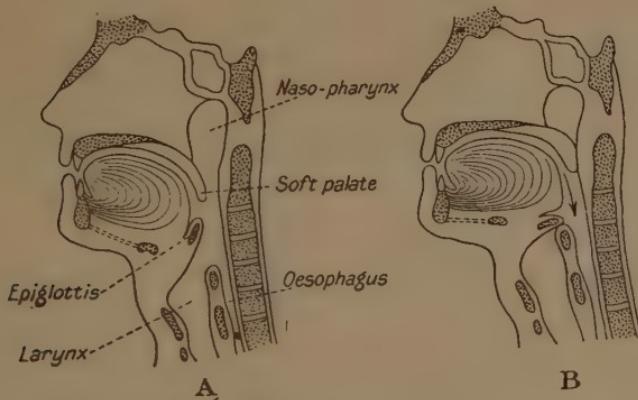


FIG. 92.—The Mechanism of the First Stage of Swallowing (Flack and Hill).

A = at rest, B = swallowing. Note raising of tongue, hyoid bone and soft palate, and closure of larynx in B.

nected with a recording tambour. Contraction of the circular muscles of the tube will press on the bag, therefore the contractions will be shown by the movements of the recording tambour.

(d) Some substance opaque to X-rays may be placed in the tube and the shadow observed on a fluorescent screen or photographed.

The last method is especially useful for following the passage of food through the human alimentary canal. It can indicate the time at which food is in certain parts of the canal and sometimes the indentation of the contents when the canal is full shows that constriction of the canal is taking place.

By these methods it has been shown that the passage of food along the alimentary canal is due to a sequence of events known as a peristaltic wave. This consists of a relaxation of circular muscle in front of the bolus and a constriction behind it. This constriction

travels along the tube pushing the contents in front of it; it is comparable to the emptying of jelly from a rubber tube by compressing the tube between the thumb and forefinger and passing them along the tube from one end to the other. Accompanying the relaxation of the circular muscle the longitudinal muscles contract, thus helping to pull the tube over the bolus as the latter is pressed onwards by the advancing wave of constriction.

This is the process by which the bolus can be passed down the oesophagus. When swallowing is occurring at short intervals the oesophagus may remain dilated so that fluids such as milk pass

down mainly by the action of gravity. The peristaltic wave in the oesophagus is dependent on nervous connections because if the muscular walls are cut across, the wave passes over the gap so long as the nerves on the surface of the oesophagus remain intact.

The movement down the oesophagus is slower than it is through the pharynx.

In the X-ray

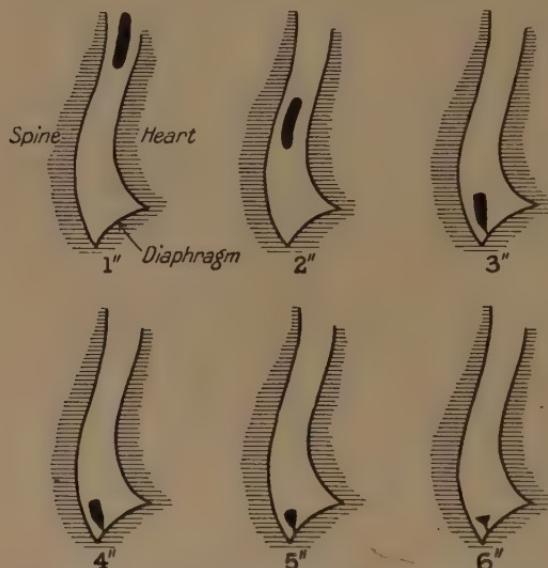


FIG. 93.—Diagram of the Position of the X-ray Shadow in Oesophagus of a Mouthful of Milk containing Bismuth at successive Intervals of a second (Hurst).

shadows, given in Fig. 93, is shown the swallowing of a mouthful of milk at one second intervals.

The shadows of the spine, heart and liver, outline the posterior mediastinum and the mouthful of milk can be seen as an opaque mass. The milk passes down as an elongated mass with rounded ends, thus showing the outline of the oesophagus. When it reaches the lower end the top becomes flat, indicating that it is at rest under the influence of gravity. The lower end is narrow and funnel shaped, indicating that the fluid is passing through a narrow sphincter. During the passage down the oesophagus the ends of the shadow are rounded, showing that the mass is falling and the shape of the ends depends upon the surface tension. On listening

at the back about the level of the twelfth dorsal vertebra a rushing sound may be heard as the liquid passes into the stomach.

### Digestion in the Stomach

After the food reaches the stomach it is permeated with an acid secretion which stops the action of ptyalin, but before the food becomes acid the ptyalin continues in action for some time.

The length of time that elapses before the food becomes acid is dependent on its quantity and its nature. As each bolus of food reaches the stomach it passes from the oesophagus so that it comes against the previous bolus. As the stomach becomes dilated with food each fresh quantity of the preceding portions are spread out over its surface. This has been demonstrated by Grützner, who fed rats on food stained with various dyes. On killing the animals and making sections through their stomachs he found that the colours remained in laminæ, so that the most recently swallowed food was contained in a layer of that previously swallowed. Therefore digestion by ptyalin will continue until the whole mass is rendered acid by diffusion of acid, and it has been stated that the ptyalin remains active for from twenty to forty-five minutes.

Whilst the food is becoming acid it is being impregnated with the other constituents of the gastric secretion, and we find that it is convenient to divide the stomach into two portions, namely the body and the pylorus. These two portions differ in the nature of their movements, histological structure and secretion.

**Movements of the Stomach.** The normal shape of the human stomach is that of a J. As liquid food enters the X-ray shadow shows that it flows mostly along the lesser curvature to the pylorus, and the stomach fills gradually from below upwards. Soon after the food enters a deep gap is seen in the lesser curvature, extending into the shadow for one-half to one inch. This is the *incisura angularis* which divides the stomach into two functional portions. Solid food, as indicated above, would lie in the main body of the stomach above the incisura. Rhythmic changes in tone occur in the body of the stomach, thus any liquefied contents are squeezed towards the pylorus.



FIG. 94.—Section of Frozen Stomach of Rat during Digestion to show the Stratification of Food given at different Times (Grützner).

The food was given in three portions and coloured differently: first, black; second, white (indicated by vertical marking); third, red (indicated by transverse marking).

Soon after a "barium" meal, wave-like gaps are seen in the greater curvature which become more marked as they move towards the pylorus. As the waves approach the pylorus they seem to cut off portions of the contents from the rest of the stomach. These waves travel at the rate of about 3 centimetres per second, and they appear at intervals of about 15 to 20 seconds. Three or four waves may be visible at one time.



FIG. 95.—Tracings of the Shadow cast by the Stomach (Cat), showing changes in the shape of the Organ at Intervals of an Hour during Digestion of a Meal (Cannon).

Such waves exercising a rowing action on the contents cause a current along the walls towards the pylorus. So long as the pylorus remains closed the contents cannot escape, so there must be a reverse current in the axis of the stomach. This mixing churning constitutes what is known as the pyloric mill. A similar movement can be seen by observing the movements of the stomach of prawns. These can be observed through the animals' transparent carapace.

TABLE XX

COMPOSITION OF GASTRIC JUICE (BIDDER AND SMITH)

|                             | Per cent. |
|-----------------------------|-----------|
| Protein . . . . .           | 1.57      |
| Hydrochloric acid . . . . . | 0.20      |
| Inorganic salts . . . . .   | 0.74      |
| Water . . . . .             | 97.49     |

One of the striking features of the gastric juice is its relatively

high concentration of hydrochloric acid. The acid has a protective action in killing bacteria and other organisms. The acid is, however, necessary for the digestive action which occurs as the result of the enzymes in the stomach. Gastric juice has a proteolytic action. It dissolves insoluble proteins such as fibrin, converting them into proteoses and peptones.

**Pepsin.** This is an enzyme which digests protein in the presence of a distinctly acid reaction. It is inactive in a neutral solution and is rapidly destroyed in faintly alkaline reaction. It is destroyed at temperatures above 60° C.

The stages of the reaction are common to all hydrolyses of protein passing through metaprotein (see Table X, page 132), primary and secondary proteoses to peptone. The quantitative methods for studying the rate of digestion have been given on p. 171. For qualitative purposes one can observe the solution of a small quantity of fibrin, and one can show the pink colour given by the proteoses and peptones with a trace of copper sulphate and alkali.

**Hydrochloric Acid.** The proof that hydrochloric acid exists in the gastric juice consists of two pieces of evidence.

(1) Some gastric juice is divided into two portions, to one of which an excess of alkali is added. These two portions are incinerated and the amount of chloride in the ash of each is estimated. The amount of chloride in the portion neutralized by alkali is greater than that in the unneutralized portion. This shows that there is some chlorine not united with a fixed base. The amount of ammonia obtainable from gastric juice on distillation with a weak alkali is not sufficient to neutralize the excess of chlorine; therefore some of the chlorine may be there as free hydrochloric acid. When protein is present some of the acid may be neutralized by it.

(2) If gastric juice is tested by indicators the concentration of hydrogen ions is greater than would be given by an organic acid.

*Methyl violet* is an indicator which shows the high concentration of hydrogen ions. With organic acids it turns blue, but with stronger acids the colour becomes green or yellow.

*Günzberg's Reagent.* This gives a positive reaction with inorganic acids, but not with organic acids. A drop of a solution of phloroglucinol (2 g.) and vanillin (1 g.) in alcohol (30 c.c.) are placed on the surface of an evaporating basin. This is spread on the surface and it quickly dries to form a varnish. One drop of the stomach contents are placed on this varnish and the whole heated over a water-bath until the drop evaporates. A bright red spot is left if an inorganic acid is present, but not if only organic acids are present.

A similar test will be given by cane-sugar and resorcinol (Boas'

reagent), and by Tropæolin OO, but the Günzberg test is the most delicate.

As the inorganic anion present in greatest amount is chlorine, we conclude that the acid is hydrochloric.

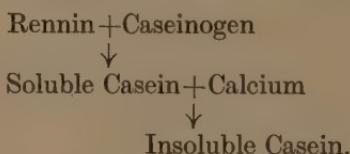
Di-methyl-amino-azo-benzol (Töpfer's reagent) and congo red both react with some organic acids ; therefore they are less satisfactory than the tests given above.

**Rennin.** In addition to the digestive action on proteins gastric juice causes coagulation of milk. This is not the same as precipitation by acid described on p. 108, as it occurs with neutral solutions. Rennin, like other enzymes, is destroyed by heating. There is one outstanding feature about its action, namely, that it requires the co-operation of calcium ions. We can show the necessity of calcium ions by the following experiment (Ringer) :—

Make up three mixtures containing : (1) milk + rennin ; (2) milk + boiled rennin ; (3) milk + potassium oxalate + rennin, respectively. No. 1 will coagulate whilst the other two do not. No. 2 fails to coagulate because the rennin had been destroyed by boiling before it was added to the milk. No. 3 fails to coagulate because the calcium salts have been precipitated as calcium oxalate.

We can show, however, that the rennin has acted on the milk in No. 3 by boiling the tube, thus destroying the rennin, and adding calcium chloride. On adding the calcium salt a coagulum is thrown down. Thus we see that the caseinogen of the milk has been altered by the rennin even in the absence of calcium ions, so that it now gives an insoluble precipitate on the addition of calcium. The change is due to the conversion of caseinogen into casein. The calcium salt of the former is soluble ; that of the latter insoluble.

The changes are indicated by the following schema :—



The action of rennin on milk presents three points of interest. First it is the process by which milk is converted into the curd, which when treated further forms cheese. Secondly, rennin is a specific test for caseinogen. Thirdly, caseinogen is a specific test for rennin.

Rennin can be extracted from calf's stomach and may be obtained separately from pepsin. The significance of this separation is that it has been claimed that pepsin and rennin are the same substance. Pepsin can be obtained free from rennin action, and

rennin can be obtained free from pepsin. Some workers deny this, but it seems fairly well established.

**Gastric Lipase.** Gastric juice acts on emulsified fats, converting them into fatty acids and glycerol. It does not act on unemulsified fats. In the later stages of digestion lipase may also regurgitate from the duodenum.

It must not be forgotten that the action of pepsin on the protein framework surrounding fat cells prepares the fat for digestion in the intestine.

#### METHODS FOR PREPARING DIGESTIVE ENZYMES

When we wish to investigate the digestive enzymes one procedure is to test their action on various substrates outside the body. In order to do this we can extract the various glands and use the extracts for digestion experiments. Extracts may be made by the use of water, salt solution or glycerol. The last is very useful in making active preparations. We may also obtain the secretion from the glands. In some cases, such as that of the saliva, it is easy to obtain the juice. One of the early methods for obtaining gastric juice is of interest. The Abbé Spallanzani (1729–1799) investigated digestion in man and animals. At the time of his experiments it was believed that digestion was due to a mechanical crushing force. Spallanzani placed food in perforated metal cylinders which were swallowed. After the tubes were recovered the contents had disappeared but the tubes had not been crushed. This showed that digestion was a chemical and not a mechanical process. He also caused the subjects of the experiment to swallow sponges tied to a string. After a brief interval the sponge was pulled up by the string and the stomach contents obtained by squeezing the sponge. In this way the digestive action was studied outside the body. The modern stomach pump consists of a rubber tube, one end of which is swallowed. It is possible to aspirate the contents from the stomach, either at one time or in small portions at a time (fractional test). One end of a long thin tube will in time pass into the duodenum, so that one can obtain samples of duodenal contents for chemical examination.

#### SURGICAL METHODS FOR STUDYING DIGESTION

The operations for obtaining juices from glands with definite ducts are comparatively easy, and were performed as early as 1664.

The opening of the parotid duct can be transferred from the inner to the outer side of the cheek. The opening of the pancreatic duct may be transferred to the abdominal wall (de Graaf, 1641–1673). A funnel and measuring cylinder suspended below the opening of

the duct is all that is necessary in order to measure the amount of secretion formed under varying conditions. The chemical action of the liquid so obtained may also be studied.

With such organs as the stomach where the secretion comes from a surface it is necessary to make a fistula. The first record of such a condition is that studied by Dr. Beaumont of Buffalo (1828). A French-Canadian was wounded in the abdomen by his own gun, and when the wound healed a permanent fistula was left. Dr. Beaumont observed the process of digestion through the opening, putting in and taking out samples through the anterior abdominal wall.

The methods elaborated by Pavlov are the foundation of most recent observations. His methods were designed with the object of obtaining the juices free from mixture with food and to trace the normal digestion of food by these juices. By means of a fistula in the stomach combined with one in the oesophagus he was able to study the effect of taking food on the secretion of gastric juice. He found that the most efficient stimulus to the secretion of gastric juice was the swallowing of food, even if the food escaped through the fistula in the oesophagus. This method of "sham feeding" proved the importance of taste on the gastric secretion. On the other hand, mechanical stimulation of the interior of the stomach (by feathers, glass rods, etc.), showed that no secretion was produced by the mere presence of solid material inside the stomach.

For continued observation of the activity of the gastric glands another type of operation was devised. This consists in the formation of a "small stomach" opening to the body surface, but isolated from the rest of the stomach. This had to be accomplished without interfering with the blood and nerve supply to the small stomach. The operation consists of an oblique incision from below upwards, through both anterior and posterior walls, along the margin of the greater curvature of the stomach. The anterior and posterior walls of the stomach are sewn together along the upper margin of the incision. The V-shaped flap along the border of the greater curvature is turned away from the stomach, and its margins sewn together to form a tubular pouch. The orifice of this tube is sewn into the abdominal wall. During the operation special care is taken to close the opening between the main stomach and small stomach, so that a layer of mucous membrane is turned with its inner surface towards the main stomach and another layer with its inner surface towards the small stomach. The mucous membrane is cut across at the base of the flap and loosened from the subjacent muscle. The cut edges are pulled across the opening, so that the two pieces of mucous membrane lie back to back. The edges are sewn to the inner surface of the stomach and to the margins of the flap respect-

ively. By this operation the blood and nerve supply of the small stomach is preserved intact.

Such a "small stomach" has been shown to correspond in activity to the main stomach. Its activity is proportional to the surfaces of the two portions, usually about one-tenth of the total stomach. The transference of the opening of the pancreatic duct to the surface of the abdomen and the opening of the gall bladder on the surface of the abdomen are obvious surgical procedures.

The small or large intestine may be opened on the surface at various parts of their courses, but in addition an isolated loop of small intestine may be made into a fistula (Thiry-Vella fistula). The method designed by Pavlov is again an improvement on the older methods. This consists in cutting through the mucous

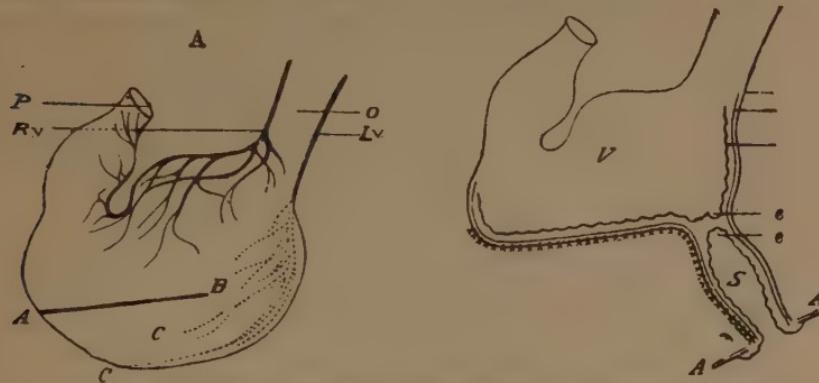


FIG. 96.—Pavlov's Method of establishing a Gastric Fistula.

*A-B* = incision, *S* = segment of stomach separated off, *A* = abdominal wall, *P* = pylorus, *O* = cesophagus, *Rv* = right vagus nerve, *Lv* = left vagus nerve, *e* = mucous membrane of stomach.

membrane, leaving the muscular and serous coats intact. The ends of mucous membrane are closed, and the intestinal tube is reformed by a lateral opening between the two intestinal ends. The central isolated portion is opened on the surface of the abdomen, so that its contents may be obtained and studied.

It is by such methods that the foundation of our modern knowledge of digestion has been laid.

During the process of secretion the changes that take place in the glands of the stomach are similar to those which occur in the salivary glands. It can be shown that pepsin is present in the glands in the form of pepsinogen. Pepsin is easily destroyed by alkali, thus if the mucous membrane of the stomach is treated with alkali all the pepsin is destroyed. On adding sufficient acid to neutralize the alkali and to form a slight excess pepsin can be shown to be present, thus indicating that pepsinogen has not been destroyed by the alkali, but has been converted into pepsin when the alkali digest is made acid.

The secretion of gastric juice occurs with a latent period of about five minutes. Cutting the vagi stops reflex secretion, whilst stimulation of the vagi causes secretion. The secretory nerves are thus shown to be the vagi. Reflex stimulation is brought about by the sight, taste, smell and thought of food. Even the sound of preparing food may cause a reflex secretion. The most efficient stimulus is that due to swallowing food as demonstrated by the "Sham feeding" experiment of Pavlov.

The microscopic structure of the two portions of the stomach shows that there are histological as well as functional differences.

The glands differ in the shape of the ducts, but the most striking difference is the presence of certain cells in the glands of the body of the stomach which stain deeply with eosin. These cells are situated on the sides of the glands away from the lumen. They are called parietal cells or, because of their staining reactions, oxyntic cells. Prolongations of the duct extend out to the parietal cells.

In addition to the oxyntic cells central or chief cells are present. As some of them are believed to secrete the enzymes, they are also called peptic cells.

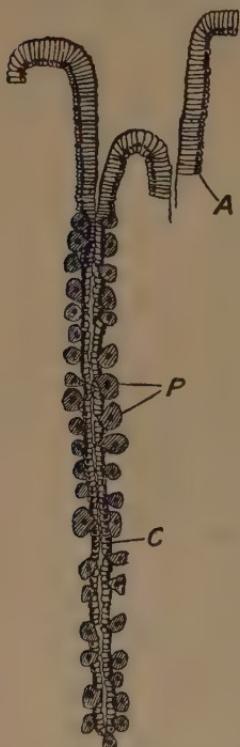
The oxyntic cells are found only in that portion of the stomach which secretes acid; hence it is believed that they are responsible for the secretion of acid. The strength of the acid when it is secreted is about 0·5 per cent. It is neutralized in the stomach, hence the strength of the acid in the juice obtained from the stomach is usually only about 0·2 per cent. After the food has been for some time in the stomach there is a

FIG. 97.—Drawing of Gland from Body of Stomach.

Note narrow lumen with central (peptic) cells and parietal (oxyntic) cells. Mucous cells may also be present with the peptic cells. *A* = columnar cells of mucous membrane; *P* = oxyntic cells; *C* = central cells.

means by which a further supply of gastric juice can be furnished. This is a chemical process of the following nature (Edkins).

An extract made from the pyloric mucous membrane by means of a solution of dextrin or other substances on injection into the blood causes a secretion of acid by the fundus of the stomach (gastrin). This indicates a process which occurs in the later stages of gastric digestion after the sensory stimuli have ceased. The substance which produces this action may be histamine.



### Passage of Food from the Stomach to the Duodenum

As one of the peristaltic waves of the pyloric mill approaches the pylorus the latter opens and allows some of the contents to pass into the duodenum. This opening is due to a balance between the acidity of the contents of the stomach and of the duodenum. Acid in the stomach favours relaxation of the pylorus, whilst acid in the duodenum causes closure of the pylorus. In fact the contraction due to acid may spread to the duodenum, so that excess of acid



FIG. 98.—Photomicrograph of Pyloric Portion of Stomach ( $\times 88$ ).

Contrast with Fig. 97. Note wide lumen and only one kind of cell.

may cause such a rapid contraction of the duodenum that some of the duodenal contents are forced back into the stomach. That something of this sort does occur is shown by the frequent if not constant presence of bile in the stomach.

The pylorus remains closed until the acid in the duodenum is neutralized by the pancreatic juice and bile. Solid particles in the stomach tend to cause closure of the pylorus. Thus during gastric digestion the solution of the solid portions and the increase in acidity tend to cause opening of the pylorus. When a small quantity of gastric contents have passed into the intestine the

pylorus remains closed until the acid in the duodenum has become neutralized. Therefore the escape of the gastric contents is gradual.

At the end of gastric digestion the pylorus relaxes sufficiently to allow solid particles to pass through. If this were not so the odd assortment of materials, such as coins, buttons, etc., sometimes swallowed would not pass through the alimentary canal, and swallowing of such articles would be a more serious accident than it is at present.

*Digestion in the stomach consists of the following activities :—*

1. Continued action of ptyalin on starch.
2. Hydrolysis of proteins by pepsin and hydrochloric acid.
3. Coagulation of milk by rennin.
4. Hydrolysis of emulsified fats by gastric lipase.
5. Some hydrolysis of cane sugar by the hydrochloric acid.

## CHAPTER XIV

### DIGESTION IN THE SMALL INTESTINE

When the acid contents of the stomach pass into the duodenum they are neutralized by the two secretions formed by the pancreas and the liver. These continue the process of digestion, and it will be more convenient to describe the digestive action of these juices and the conditions under which they pass into the duodenum before we deal with the more complicated conditions in the intestine.

#### Pancreatic Juice

The digestive action of pancreatic juice is due to the following enzymes : amylopsin, trypsin, lipase and a rennin-like enzyme.

*Amylopsin or Pancreatic Amylase.* This is an enzyme which resembles the ptyalin of saliva. The differences which are said to distinguish it from ptyalin are that it can act on uncooked starch, whereas ptyalin can act on starch only after the starch grains have been split by cooking, and that it may produce glucose, whereas the action of ptyalin stops at the stage of formation of maltose. The second difference may be due to the presence of a second enzyme, maltase, which converts maltose into glucose.

The optimum hydrogen ion concentration for the action of amylopsin is near to the neutral point : the optimum temperature is about 42° C. The enzyme is rapidly destroyed at temperatures above 60° C.

*Trypsin.* This enzyme hydrolyzes proteins ; it differs from pepsin in two ways. Firstly, it does not act in an acid medium, but only in an alkaline reaction. Secondly, it carries the digestion to a further stage of hydrolysis ; thus it does not cease its action when the proteins are converted into proteoses and peptones, but the action is carried on to the stage of formation of some polypeptides and amino acids. This may, however, be due to the presence of a second enzyme, erepsin (see later).

The maximum activity is in a concentration of hydrogen ions about  $1 \times 10^{-9}$ —that is, on the alkaline side of neutrality.

*Lipase.* The action of this enzyme is to convert fats into fatty acids and glycerol. Its maximal activity is in slightly alkaline solution.

The rennin-like enzyme is not of much importance.

The changes in the gland cells of the pancreas during secretion

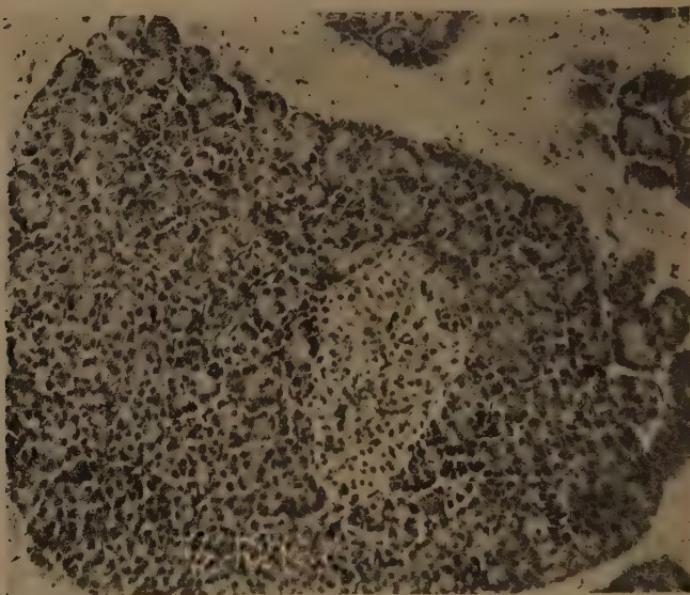


FIG. 99.—Photomicrograph of Pancreas ( $\times 100$ ).

An islet of Langerhans is seen surrounded by the secreting tubules of the gland.

are similar to those described in the salivary and gastric glands (see Fig. 100).

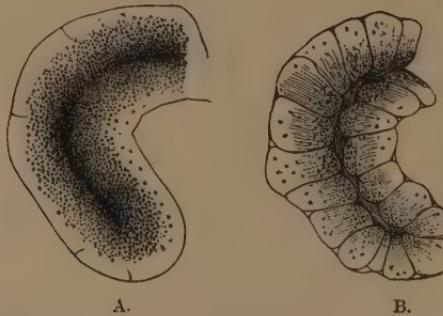


FIG. 100.—Serous Gland. Rabbit's Pancreas observed during Life  
(Kühne and S. Lea).

A. Resting. Outer clear zone (protoplasm), inner granular zone (zymogen). B. Active. Increase of outer zone, decrease of inner zone (discharge of zymogen). (From Waller's *Human Physiology*, Longmans, Green & Co.)

**The Secretion of Pancreatic Juice** is mainly the result of a chemical process. The presence of acid in the duodenum

causes a secretion of pancreatic juice even after the nerves to the pancreas are cut (Popielski). This observation led Bayliss and Starling to test the effect of making an acid extract of the small intestine and to inject this extract into the blood. They found that if the mucous membrane of the duodenum is boiled with dilute hydrochloric acid and the extract neutralized and injected into the blood a copious secretion of pancreatic juice occurred. This can only be due to a chemical substance which passes by the blood to the cells of the pancreas. They introduced the name *secretin* for this substance, and the group of such chemical stimulants they called *hormones*. As we have seen, Edkins later discovered a similar substance which stimulates the secretion of gastric juice ; this he called *gastrin*. Histamine, however, seems to have an action similar to that of gastrin. Although the main stimulus to the secretion of pancreatic juice is secretin stimulation of the vagi nerves can cause some secretion by the gland.

The juice obtained from the pancreatic duct is, however, without action on proteins and becomes active only after it passes into the intestine. Thus we meet a further complication that the juice must be activated, i.e. the trypsinogen of the juice must be converted into trypsin. The necessity for postulating trypsinogen in the pancreatic juice makes it necessary to assume that in the gland cells there exists a substance which is converted into trypsinogen during secretion.

**The Activation of Trypsinogen.** This can be brought about in two ways, namely by an extract of the intestine or by the addition of calcium chloride.

The former action is due to an enzyme which is called enterokinase, the suffix *-kinase* indicating an enzyme that acts on an enzyme. That enterokinase is an enzyme and does not act merely by uniting with trypsinogen is shown by the fact that the enterokinase is destroyed by heating to boiling and that the amount of digestive activity is independent of the amount of enterokinase added, provided that the enterokinase is allowed to act on the trypsinogen for a sufficiently long time.

The mode of action of calcium chloride (Delegenne) is not quite clear, but it may be that there is some enterokinase in pancreatic juice which does not act because of the alkalinity of pancreatic juice. When calcium chloride is added to the juice calcium carbonate is precipitated and sodium chloride formed : thus the alkalinity of the juice is reduced.



TABLE XXI  
COMPOSITION OF PANCREATIC JUICE (DE ZILWA)

|  |               |
|--|---------------|
| Total Solids . . . . .                   | 1·6 per cent. |
| Total protein . . . . .                  | 0·5 "         |
| Ash . . . . .                            | 1·0 "         |
| Chlorides . . . . .                      | 0·28 "        |
| Alkalinity 10 c.c. = 12·7 c.c. N/10 HCl. |               |

The sodium carbonate stated to be present in the juice may be secreted in the form of bicarbonate and carbon dioxide may have been lost before it was analyzed.

### Bile

The composition of bile varies considerably according to whether it is collected during an operation or from a fistula after the bile has been escaping from the body for some time. Specimen analyses of human bile are given below.

TABLE XXII  
COMPOSITION OF HUMAN BILE (ROSENBLoom)

|                              | Bladder Bile.  | Fistula Bile.  |
|------------------------------|----------------|----------------|
| Bile Salts . . . . .         | 9·70 per cent. | 1·01 per cent. |
| Mucin and pigments . . . . . | 4·19 "         | 0·49 "         |
| Cholesterol . . . . .        | 0·99 "         | 0·26 "         |
| Fat . . . . .                | 0·19 "         | 0·69 "         |
| Soaps . . . . .              | 1·12 "         | 0·26 "         |
| Lecithin . . . . .           | 0·22 "         | 0·64 "         |
| Total solids . . . . .       | 17·03 "        | 2·98 "         |
| Inorganic matter . . . . .   | —              | 0·92 "         |
| Fatty acids . . . . .        | —              | 0·12 "         |
| Water . . . . .              | 82·97 "        | 97·02 "        |

Bile fulfils a two-fold function, namely secretion and excretion. The former is of main interest in the present chapter; the latter must be dealt with more fully later (see p. 271).

Bile aids the digestive activity of the pancreatic juice. It does this by helping to neutralize the acid chyme escaping from the stomach, and by the physico-chemical properties of the bile salts, but bile possesses no digestive enzymes of its own.

The bile salts owe their action to their property of decreasing the surface tension, not only at an air-water surface but also at a fat-water surface. By decreasing the surface tension the fat is more easily converted into an emulsion. By increase in the fineness of subdivision the surface of the fat is increased. Since the action of an enzyme on an insoluble substance must be on the surface, this increase in surface accelerates the rate of hydrolysis of fats.

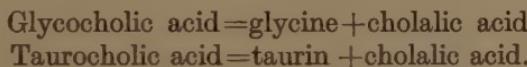
Although the main action of bile is on the digestion of fats, the digestion of carbohydrates and of proteins is also accelerated. If a

duplicate series of tubes are prepared with digestive mixtures of pancreatic juice and food substances, and to one tube of each pair a little bile is added it will be found that the rate of digestion is increased. A control series of the same food materials and bile without pancreatic juice shows that the bile by itself is without digestive action.

### Chemistry of Bile Salts

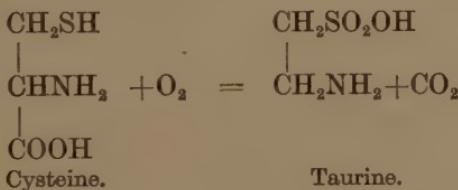
These are the sodium salts of two acids, namely, glycocholic and taurocholic acids. These occur in different proportions in the bile of different animals. For instance, dog's bile contains only sodium taurocholate, whilst human bile contains both salts.

These two acids are easily hydrolyzed, yielding simpler products as follows :—



Cholic acid has the empirical formula of  $C_{24}H_{40}O_5$ , and it is somewhat allied to cholesterol ( $C_{27}H_{47}O$ ) which also occurs in bile. The source of cholic acid is not known but one is tempted to emphasize its similarity to cholesterol.

The amino-acid glycine is obtained by the breakdown of proteins, and the taurine is also derived from proteins through the amino acid cysteine.



*Pettenkofer's Test.* One of the reactions for bile salts is due to the presence of cholic acid. To a solution containing bile salts a little cane-sugar is added, the solution is shaken until a froth is formed, then concentrated sulphuric acid poured into the tube to form a layer below the mixture of cane-sugar and bile salts. A purple ring is formed and a purple streak where the acid has passed through the froth. The test is due to the formation of furfural from the sugar which reacts with cholic acid to give a purple colour. This test is given by other substances, notably some that occur in urine.

*Oliver's Test.* Another property of bile salts is that they precipitate meta-proteins and proteoses in an acid solution. The cause of this precipitation is not known, but it occurs when bile comes into contact with the acid chyme and it is used as a test for bile salts in urine.

The bile salts markedly decrease the surface tension of water at an air-water surface. This property can be used as a test for the presence of bile salts in urine and, as mentioned above, it is an important factor in the digestion of fats by pancreatic juice.

There are many methods for the estimation of surface tension, but the most convenient is the stalagmometric method. The principle involved is that a drop falls from the end of a special pipette when its weight is sufficient to overcome the adhesion of the column of liquid and the surface tension of the circumference where the drop joins the pipette. In practice a known volume of liquid is allowed to flow slowly through a tube and the number of drops that it gives rise to is counted. The weight of liquid is measured by multiplying the volume by its specific gravity. The weight of each drop is the total weight of liquid divided by the number of drops. The surface tension of the liquid is usually compared with that of water as unity. In this case the specific gravity of water being also unity, one calibrates the pipette by counting the number of drops formed when water runs out of the pipette and uses that number to compare with the number of drops formed by the liquid containing bile salts. Therefore the surface tension as compared with that of water is

$$\frac{\text{Number of drops of water} \times \text{specific gravity of the solution.}}{\text{Number of drops formed by the solution.}}$$

This is a quantitative development of *Hay's test*. The latter is carried out by sprinkling sublimed sulphur on the surface of the liquid. The weight of the finely divided sulphur is such that it breaks through the water surface very slowly, but if the surface tension is decreased the sulphur sinks rapidly to the bottom of the vessel containing the liquid.

Bile salts are not lost but reabsorbed and passed back to the liver (see p. 271). Thus we believe that bile salts are largely reabsorbed and rescreted by the liver and comparatively little of them is lost in the faeces : bile salts are not found in faeces except when the intestinal contents have been hurried through the bowel, as, for instance, by a purgative.

**Properties of Bile Pigments.** Two coloured substances are found in bile, namely bilirubin and biliverdin. The former is an orange-coloured substance which is predominant in the bile of carnivora : the latter is greenish in colour and gives the colour to the bile of herbivora.

*Gmelin's Test.* These pigments are recognized by colour reactions of which the best known is the series of colours given by bile pigments with nitric acid. This can be carried out by bringing the bile pigments and nitric acid in contact either in a test tube, on a

piece of filter paper or on a glazed porcelain surface. The colours range, through green, blue, violet, red and yellow, from the solution of bile pigment to the nitric acid. Of these the green colour is the most characteristic.

*Iodine Test.* Another test is the green colour given by bile pigments with a solution of iodine in potassium iodide.

Both these tests are the result of oxidation of the bile pigments.

*Hupper's Test.* When the concentration of bile pigments is low, as when testing for bile pigments in urine, they may be precipitated and thus concentrated. To the urine is added a solution of calcium chloride followed by ammonia. The solution is centrifugalized and the precipitate is washed by suspending it in distilled water and recentrifugalizing. The bile pigments are carried down with the precipitate as calcium bilirubinate. By extracting the precipitate with alcohol containing hydrochloric acid and an oxidizing agent ( $KClO_3$ ) the bile pigments dissolve to give a green colour to the alcohol extract.

The bile pigments are derived from the blood pigment, thus their chemistry will be dealt with in connection with the derivatives of haemoglobin. In the intestine they are reduced to stercobilin, some of which is absorbed and excreted in the urine as urobilin or urobilinogen.

**The remaining Constituents of Bile.** Like other body fluids bile contains salts, but there are several other substances which require mention. Soaps (other than the bile salts) are present, but their function is unknown, unless it is to act like the bile salts in decreasing the surface tension. Lecithin is present also, but its significance is unknown. Cholesterol is present in an appreciable quantity. It is apparently a necessary constituent of all cells and it is the excess which is passed out in the bile (Gardner). The possible relation of cholesterol to cholic acid has been pointed out above (p. 191). Cholesterol is insoluble in water, but it is held in solution in the bile by the bile salts. If the amount of cholesterol is excessive or the amount of bile salts deficient cholesterol is precipitated, and it may form concretions known as gall stones. The precipitation of cholesterol is frequently regarded as the result of infective processes in the gall bladder.

**Formation of Bile.** As bile is not merely a digestive secretion we find that its formation is not confined to the periods of digestive activity. The bile formed between the times when bile is poured out into the intestine is stored in the gall bladder ; it is interesting that the horse, in which digestion is practically continuous, has no gall bladder.

During digestion the rate of formation of bile is increased. This increase may be due to secretin acting on the cells of the liver

in addition to those of the pancreas, but all the activities of the liver are increased during absorption of food, and the increased formation of bile may be partly a result of this increased activity, perhaps as the result of an increased blood flow and unabsorbed bile salts.

**Passage of Bile into the Intestine.** Although the formation of bile is more or less continuous, the passage of bile into the intestine is partly related to the passage of food from the stomach to the duodenum. Thus, if a constant pressure of fluid be maintained in the bile duct and the rate of passage of fluid into the intestine is measured, it is found that filling the stomach decreases the rate of escape and emptying the stomach causes an increased passage of fluid from the bile duct. There is no doubt that escape of bile may be aided by the contraction of the musculature of the gall bladder.

#### COMBINED ACTION OF PANCREATIC JUICE AND BILE.

The acid chyme is neutralized by the combined action of these two juices. The polysaccharides, proteins and fats are hydrolyzed by the pancreatic juice aided by the bile. Precipitation of proteoses by bile salts may be of use in delaying the onward passage of these substances, so that the pancreatic juice may act on them more efficiently. The resultant products of the combined action of bile and pancreatic juice are maltose, proteoses, peptones, polypeptides, amino acids, fatty acids and glycerol.

**Further Hydrolysis in the Intestine** is the result of enzymes obtained from the cells of the intestinal mucosa of which the following have been recognized :—

TABLE XXIII  
ENZYMES OF SMALL INTESTINE

*Maltase* acts on maltose producing glucose.

*Lactase* acts on lactose producing glucose and galactose.

*Invertin* or *sucrase* acts on sucrose producing glucose and fructose.

*Erepsin* acts on proteoses and peptones producing amino acids.

Erepsin is present in all living cells ; it is without action on most proteins, but acts on protein derivatives. Two proteins are known to be acted on by erepsin, these being fibrin and caseinogen.

Various types of fistulae have been made, to investigate the digestive processes in the small intestine.

A length of intestine with a single opening to the surface and the other end open is known as a Thiry fistula. A Thiry-Vella fistula differs from the above in that both ends of the length open on the surface. The two ends of the cut intestine are united to restore the continuity of the intestine. When the nerve supply of

the intestine is interfered with excessive escape of fluid occurs into the denervated section. Pavlov's operation for fistula gives a better result as the nerve supply is less injured (see p. 183).

An extract from the mucous membrane of the intestine usually shows a greater degree of enzyme activity than the intestinal juice ; therefore it is assumed that the enzymes are contained in the cells and are not so freely secreted as, for example, the enzymes of the pancreas.

The amount of intestinal juice increases a few hours after a meal, and the increase may be due to secretin acting on the intestinal glands in addition to those of the pancreas and liver.

As a result of the various digestive processes described in this and the preceding chapter, the insoluble or colloidal food substances are formed into simple substances, most of which are soluble and diffusible. The soluble diffusible substances consist of mono-saccharides, amino acids and glycerol. The insoluble products of fat hydrolysis, namely fatty acids, can form soluble soaps with alkali and the fatty acids themselves can be held in solution by the bile salts.

Before discussing the digestive processes in the large intestine it is necessary to study the absorption of food in the small intestine, as the digestion in the large intestine must be governed by the material passed on to it from the small intestine.

## CHAPTER XV

### ABSORPTION FROM THE SMALL INTESTINE ABSORPTION

The absorption of food materials from the small intestine is intimately related to the structure of the absorbing wall. From the physical point of view the thinner the absorbing layer the more rapid the process of diffusion and the greater the extent of surface the more rapid will be the absorption. As the absorbing surface consists of columnar cells it appears as if something more than diffusion occurs.



FIG. 101.—Photomicrograph of longitudinal section of villi ( $\times 88$ ).

The columnar epithelial cells with occasional mucous (goblet) cells are visible. The narrow cleft of the central lacteal is seen in the centres of the villi.

increase in surface in proportion to the surface of the projection to its base. In the case of a cylindrical villus such as one from the duodenum or upper portion of the jejunum the surface is area

of sides of cylinder + area of one end of the cylinder, whilst the area of mucous membrane corresponding to the base is equal to the area of one end of the cylinder. The increase in area is therefore in the ratio of  $2\pi lr + \pi r^2$  to  $\pi r^2$  or as  $2l + r : r$ .

Krogh has calculated that with sixteen villi to each square millimetre of surface and with villi 0.5 to 0.6 mm. long and 0.2 to 0.25 mm. in diameter, for each square millimetre of intestinal surface there will be 7 sq. mm. of surface of villi. With less regularly shaped villi the calculation is not so simple.

**The Structure of the Villi** is important as they are the main channels of absorption.

Each villus is covered by a layer of columnar epithelial cells, which is supported on a core of areolar connective tissue. Underneath the epithelial cells is a network of blood capillaries. In the centre of the villus is an open space which represents the blind ending of the lymphatic system. Thus they are the channels by which food materials may pass from the villus:—

(a) By the blood-vessels through the mesenteric veins to the portal vein and liver.

(b) By the lymphatics to the receptaculum chyli, up the thoracic duct to the vascular system at the junction of the subclavian and internal jugular veins.

Absorption may take place from any surface as can be shown by painting the surface with some easily diffusible substance. Thus it can be shown that if the skin is painted with iodine, the iodine can soon be demonstrated in the urine. However, absorption from the mouth is negligible and from the stomach it is only slight. Alcohol can be absorbed from the stomach more rapidly than water.

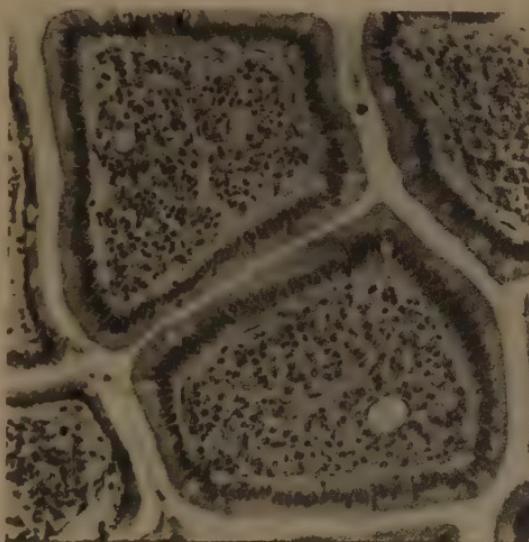


FIG. 102.—Photomicrograph of Cross Section of two Villi ( $\times 100$ ).

The lacteal is clearly seen and the columnar cells with occasional goblet cells are visible.

### Absorption from the Intestine

If an animal is given a meal containing fat and after several hours the animal is killed and its abdomen is opened the mesentery will show a number of white lines. These are the lymphatics filled with fat. By collecting some of the lymph and analyzing it, it is found to be an emulsion of neutral fat. If the fat in the food had been stained with an absorbable dye the lymphatics would have been coloured by the colour of the fat-soluble dye.

Owing to the milk-like appearance of the lymph in the lymphatics of the mesentery during the absorption of fat these vessels are called lacteals.

The insolubility of the fat renders it easy to trace the path of its absorption so that it can be followed up the thoracic duct to the

opening of the latter into the venous system. In fact Munk found that in a girl with a lymphatic fistula 60 per cent. of the fat given by the mouth could be recovered from the opening of the fistula within twelve hours of taking the food.

After a meal containing fat the animal's abdomen may be opened and the intestine fixed. If this material be examined it is possible to see the fat in the epithelial cells. In the cells it is visible as fine droplets in the inner two-thirds whilst the outer third contains larger globules. Analysis

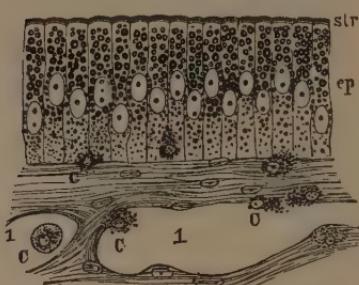
FIG. 103.—Mucous Membrane of Frog's Intestine during Fat-Absorption.

*ep* = epithelium, *str* = striated border, *C* = leucocytes, *l* = lacteal. The fat-particles have been stained black by osmic acid.  
(From Schafer's *Essentials of Histology*, Longmans, Green & Co.)

of the intestinal contents shows that the fat is mainly in the form of fatty acids whilst we have seen that the lymph in the lacteals contains the neutral glycerides.

It is deduced that the fatty acids are absorbed and turned into glycerides in the intestinal epithelium. A further proof that the epithelial cells can form glycerides is that if an animal is fed on fatty acids, neutral fat is still found in the lacteals. In this case glycerol must be formed in the cells, probably from glucose.

It is believed that the fatty acids are absorbed in solution because the outer striated margin of the cells does not contain any highly refractile granules. Fatty acids can be absorbed in solution as soaps or held in solution by the bile salts. All the fatty acids cannot be in the form of soap because the intestinal contents are acid to phenolphthalein (Moore), but it is possible that in the



cells the alkali of the protoplasm will form soaps from the fatty acids.

That the bile salts are of considerable importance in the absorption of fats is shown when the bile salts are excluded from the alimentary canal. Under such circumstances the fat is not adequately absorbed and it appears in the faeces, giving them a chalky white appearance because of the large amount of highly refractile material in the form of fat globules. In some cases the non-absorption of fat is not due to deficient hydrolysis, because it is present in the form of free fatty acid, i.e. the pancreatic lipase has hydrolyzed the fat, but the fatty acid has not been absorbed.

The absorption of fatty acid is influenced by the bile salts probably because they decrease the surface tension between the fatty acid and the epithelial cells. By decreasing the surface tension these two are brought into more intimate contact so that absorption can take place. This is analogous to the fact that ink will not adhere to the greasy surface of tracing paper except in the presence of bile salts.

Unless the substance wets the surface it cannot be absorbed, hence the importance of bile salts in causing fatty substances to wet the intestinal surface.

In coeliac disease the failure to absorb fat may be due to the absence of bile salts as the faeces contain fatty acids, thus showing that the fats have been hydrolyzed. Administration of bile salts has caused an improvement in some cases (Miller).

Carbohydrate and protein are not absorbed by the same channel as the fats. This can be shown by examining the lymph from the thoracic duct during the absorption of carbohydrate and of protein. The amount of these substances found in the lymph from the thoracic duct is inconsiderable. Some other path must exist for the absorption of these substances and this must be the blood stream.

**Absorption of Carbohydrates.** That carbohydrates are absorbed by the blood stream is shown by an increase in the amount of glucose in the portal blood as compared with that in the blood going to the intestine during the absorption of carbohydrate. This glucose is stored in the liver in the form of glycogen. The deposition of glycogen in the liver can be shown by contrasting the liver of an animal which has not been fed recently with that of one which has had a meal rich in easily absorbable carbohydrate about four hours previously. Another proof that this glycogen is formed from sugar in the portal blood is that when the portal blood is bringing extra sugar to the liver the hepatic blood from the hepatic veins contains less sugar than the blood passing to the liver. Disaccharides are absorbed much less rapidly than hexoses.

**Absorption of Proteins.** The proteins are hydrolyzed to amino acids, hence it is the absorption of amino acids and their fate which is of interest. That amino acids are present in circulating blood is shown by the experiment of Abel, Rowntree and Turner. These workers passed blood through a series of collodion tubes surrounded by saline. A series of sixteen tubes passed through a container and they were connected so that the blood passed through eight tubes and back by the remaining eight. Amino acids were found in the saline surrounding the tubes, i.e. amino acids were present in the circulating blood and they dialyzed through the collodion tubes into the surrounding saline.

Thus we see that any simple diffusible substances formed in the small intestine are absorbed. The process of absorption may be either simple diffusion or it may require an expenditure of energy. Discussion of these processes must be deferred until a later chapter. There are so many factors common to absorption, excretion and secretion that it will be more convenient to discuss these together.

### MOVEMENTS

During the processes of digestion and absorption the contents are moved along the intestinal canal and kept mixed by the activities of the involuntary muscles of the intestine.

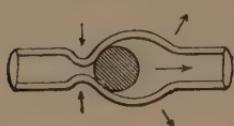
**Peristaltic Movements.** The contents are moved onwards by a process which has been mentioned in relation to swallowing. The contents of a tube can be forced out by means of a piston. In the case of a muscular tube constriction of the circular muscles closes the tube and such a constriction if it travels along the tube will have the same effect as a piston. The movement of peristalsis is not quite so simple because the part of the intestine which is

about to receive fresh contents can be expanded because its muscular coat relaxes. It is also stated that the longitudinal muscles contract when the circular muscles relax, thus drawing the dilated portion up to the constricted section. Peristalsis may be therefore defined as a wave of relaxation followed by a wave of constriction travelling along a muscular tube. The methods used

FIG. 104. — Diagram showing Peristaltic Contraction of Intestine (Cannon).

to investigate movement of a hollow tube are given on p. 175.

The rate at which the wave travels is frequently about 2-3 cms. per minute. Sometimes more rapid waves occur but these more rapid waves will be considered in relation to the large intestine. The wave usually travels in an aboral direction. If a segment of small intestine is cut at each end and the two ends sutured



to the rest of the intestine so that this segment is reversed in direction a form of partial intestinal obstruction results. The peristaltic wave in the reversed segment delays the passage of the contents along the tube. That the contents can pass in the wrong direction is shown by the faecal vomiting of acute intestinal obstruction.

The peristaltic wave is produced in the intestine itself and is not due to nervous impulses from the central nervous system. This can be shown either by cutting the nerves in an animal or even removing the intestine from the animal and observing the movements when its intestine is suspended in warm oxygenated Ringer Solution.

The movements are however regulated through nervous control. The nervous mechanism of the movement and the control of the movements will be discussed later (see p. 482).

**Segmentation Movements.** When a portion of the intestine is observed by X-rays it may be seen to divide into a series of segments. These segments coalesce and fresh divisions appear between the previous constrictions.

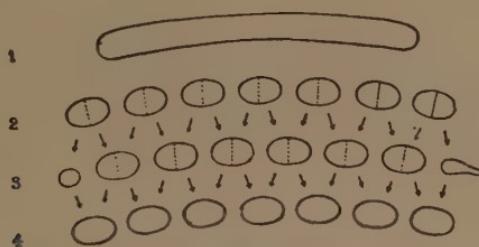


FIG. 105.—Diagram representing the Process of Rhythmic Segmentation (Cannon).

Lines 1, 2, 3, 4 indicate the sequence of appearance of a single loop. The dotted lines represent the regions where division is about to occur. The arrows show the relation of the parts of the loop to the segments which they subsequently form.

These appearances are due to a series of constrictions of the circular muscular coat. These constrictions disappear but contraction occurs at another place. The result of these constrictions is that the semi-solid contents are mixed just as dough is mixed by kneading it. Dough is too stiff to be stirred but continuous pushing and punching it mixes it thoroughly.

It is not quite clear that these regular constricting movements are the same as those rapid waves of constriction which pass over the intestine at the rate of 5 cms. per second (*pendular movements*).

**Vermicular Movements.** If semi-solid or liquid material were passed through a mass of thin walled rubber tubing any kinks in the portion filled with contents would straighten out. This alteration in position must occur as contents pass from one part of the intestine to another. In fact worm-like movements of the intestine

may be observed when the abdomen of an animal is opened. The suspension of the small intestine by the mesentery and the smooth layer of peritoneum covering the intestine both facilitate the sliding of the coils of intestine over each other.



FIG. 106.—Photograph of the Small Intestine during the Process of Segmentation (Cannon).

As the result of the segmentation movements and the peristaltic waves the intestinal contents are thoroughly mixed with the secretions of the alimentary canal. As absorption continues fresh portions of the contents are brought into contact with the absorbing surfaces. Ultimately the contents reach the ileo-cæcal sphincter. The absorbable constituents have been mostly absorbed but the consistency is still semi-liquid.

The ileo-cæcal band of muscle relaxes from time to time as a peristaltic wave approaches it. Some of the contents are forced into the cæcum in the same way that stomach contents are forced into the duodenum.

## CHAPTER XVI

### DIGESTION AND ABSORPTION IN THE LARGE INTESTINE

Under normal conditions the intestinal contents that pass from the small to the large intestine have had nearly all digestible material digested and absorbed in the small intestine. The contents are still liquid because the absorption and secretion of water has kept pace with the absorption of the digested products. Thus the percentage of water is the same although the total quantity may be less.

In the large intestine a further amount of water is absorbed and the food materials are further acted on.

The first point to be mentioned is that there is a delay in the onward passage of the contents. In the cæcum there is a reverse peristalsis so that waves of contraction pass down from the hepatic flexure of the colon towards the ileo-cæcal valve. Thus, as in the stomach, there is a flow of contents down the sides of the cæcum. As the contents cannot pass back to the ileum because of the ileo-cæcal valve and the ileo-cæcal sphincter, there is a return axial flow up the ascending colon. This delay and mixing gives further time for the continued action of the enzymes carried on from the small intestine, but it is probably of more importance in connection with the digestion of cellulose.

Mammals possess no ferment capable of hydrolyzing cellulose, but lower animals (e.g. snail) can digest cellulose. The higher animals make use of bacteria for the hydrolysis of cellulose. In ruminants the bacterial digestion takes place during chewing the cud and whilst the food material is remaining in the rumen. In other animals, such as the horse, bacterial digestion takes place in the cæcum.

In man it is probable that a certain amount of bacterial digestion of cellulose occurs in the cæcum. By this digestion the cellulose gives rise to gases such as methane and carbon dioxide and to organic acids which can be absorbed and used by the body. Methane can be demonstrated in the expired air of herbivora. Not only is the cellulose in this way rendered available for digestion, but also the contents contained in the cellulose envelopes of plant cells are

set free. These can be digested by the enzymes which are still present in the intestinal contents.

Bacteria, however, may act on other substances than cellulose. Amino acids may be attacked producing bases by decarboxylation or hydroxy acids by deamination. This is known as bacterial putrefaction.

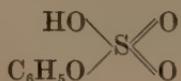
— CH(NH<sub>2</sub>)COOH with the loss of carbon dioxide gives — CH·NH<sub>3</sub> and — CH(NH<sub>2</sub>)·COOH with the addition of water gives — CHOH·COOH and NH<sub>3</sub>.

Aromatic and heterocyclic amino acids may be destroyed so as to leave the aromatic or heterocyclic nuclei. Phenyl alanine and tyrosine may give rise to phenol and tryptophane may give rise to indol and skatol. These products of bacterial action are partly absorbed and some of them are toxic.

We find that the body may defend itself from toxic substances in several ways. If the cells are unable to oxidize the toxic substance it may be united with something else to form a non-toxic compound.

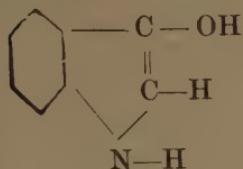
In the urine we found an example of this process of conjugation in which benzoic acid became united with glycine to form hippuric acid. This conjugation is brought about by the kidney.

In the case of phenolic substances we find that they can be united with sulphuric acid to form conjugated sulphates. The conjugated sulphates are recognized by the fact that they do not form insoluble barium salts. If all the inorganic sulphates are precipitated from urine by barium chloride and the clear filtrate is hydrolyzed by acid a further precipitate of barium sulphate is formed. This is due to the sulphuric acid liberated by hydrolysis from the conjugated sulphates. An example of a conjugated sulphate is phenol sulphuric acid

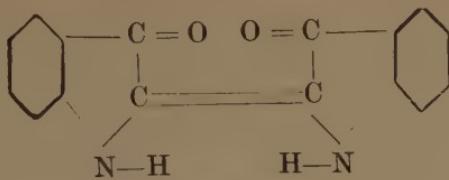


Another example is indole sulphuric acid which is found in the urine as the potassium salt (urinary indican). By hydrolysis of urinary indican indoxyl is formed which by a mild oxidizing agent is converted into indigo blue.

The colour may be used for a colorimetric estimation of the indican. Skatole, which is methyl indole, behaves like indole, but the colour given when skatole is oxidized is a reddish purple. It is important to remember that these conjugated sulphates give an indication of the bacterial putrefaction in the intestine. Other substances such as hydrogen sulphide may be formed by the action of bacteria on proteins.



Indoxyl.



Indigo blue.

Absorption and digestion are not of much importance in the large intestine. Nutrient enemata are valuable mainly as a supply of water and not as a source of food. The large intestine has an excretory function, and it seems to play an important part in the excretion of calcium, magnesium, iron and phosphates.

The mucous membrane of the large intestine is characterized by the multitude of mucus-secreting goblet cells. This points to the importance of lubrication as the contents become more solid.



FIG. 107.—Photomicrograph of Large Intestine ( $\times 88$ ).

Note large number of mucus-secreting (goblet) cells.

### Movements of Large Intestine

After the contents have been well churned in the cæcum an occasional peristaltic wave carries some of the contents along the transverse colon. During their passage across the transverse colon water is absorbed so that the contents become of a firm consistency by the time that they reach the splenic flexure. The contents aided by gravity pass down the descending colon to collect in the sigmoid flexure.

The large intestine is not so freely movable as the small one. The ascending and descending colons cannot move about like the various parts of the small intestine. Segmenting movements are not seen in the large intestine.

### Defæcation

If a small quantity of the contents of the sigmoid flexure are passed into the rectum the desire for defæcation is aroused. The

contents pass beyond the pelvi-rectal flexure only at infrequent intervals and the rectum is usually empty.

The stimulus is due to the distension of the rectum as blowing up the rectum with gas produces the same sensation. If defaecation does not occur the rectum relaxes and the desire to defaecate passes off. Defaecation is brought about partly by a voluntary effort. The glottis is closed and the diaphragm forced downwards. The increased intra-abdominal pressure helps to force some contents from the sigmoid flexure into the rectum. The rest of the process is a reflex which causes an emptying of the greater part of the ascending colon and possibly part of the transverse colon.

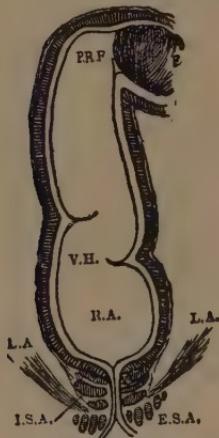


FIG. 108.—Diagram of Rectum (Hurst), showing Pelvi-Rectal Flexure (P.R.F.); Faeces in Colon (F.); Houston's Valve (V.H.); Rectal Ampulla (R.A.); Levator Ani (L.A.); Internal Sphincter (I.S.A.) and External Sphincter (E.S.A.).

Note that the rectum is empty. When contents enter it the desire for defaecation is felt.

2. Undigested material, i.e. the portions of the food substances which have not been digested and absorbed.
3. Epithelial cells and mucin from the intestine.
4. Inorganic salts, e.g. calcium, magnesium, iron and phosphates excreted by the intestine.
5. Bacteria, most of which are dead.

The amount of nitrogen in faeces is about 1 per cent., most of which is contained in the bodies of the bacteria.

On a mixed diet about 35 gms. of dry material and about 100

The process whereby the large intestine is emptied is a rapid wave of contraction which passes over the greater part of the colon. This is called a "rush" peristalsis. The characteristic feature of the movements of the large intestine as seen by X-rays is the way in which the contents appear stationary for a long time, then a sudden change occurs showing that the contents have been moved suddenly. Defaecation shows this very clearly. "Rush" peristalsis sometimes occurs in the small intestine. Fig. 109 shows the average times at which contents reach the various parts of the large intestine after a bismuth (or barium) meal.

The faeces contain undigested and indigestible matter with the bodies of dead and living bacteria. The composition of faeces is as follows:—

1. Indigestible material, i.e. woody fibre or anything not acted on by the digestive juices.

gms. of water are passed daily by the faeces. On a diet containing much coarse vegetable fibre the quantities are 75 and 260 gms. respectively.

Thus we see that a small quantity of carbohydrate fat and protein escape digestion and absorption. This amount varies with the nature of the food. Coarse indigestible food yields a larger

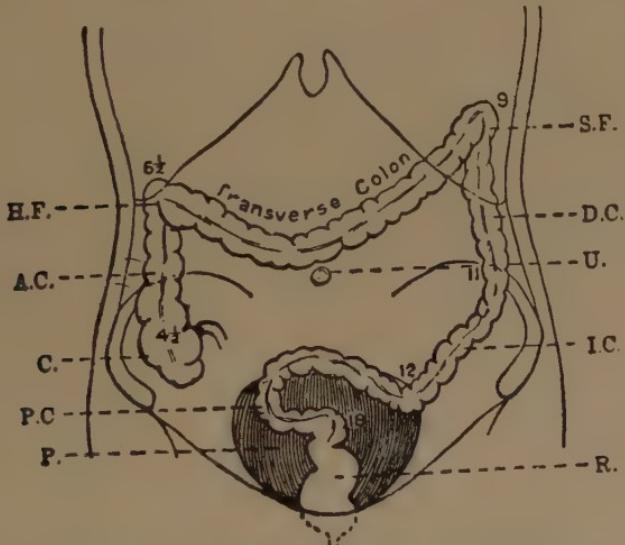


FIG. 109.—Diagram to show the Hours which elapse after a Bismuth Meal before the Different Parts of the Colon are reached (Hurst).

P. = Pelvis, P.C. = Pelvic colon, C. = Cæcum, A.C. = Ascending colon, H.F. = Hepatic flexure, S.F. = Splenic flexure, D.C. = Descending colon, U. = Umbilicus, I.C. = Iliac colon, R. = Rectum.

amount of waste food materials. The importance of this loss is that in considering the energy value of the food to the body any loss by the faeces must be subtracted from the food intake before the net food value can be measured.

It is usual to make an analysis of faeces in metabolism experiments. Most of the nitrogen in the faeces is in the bodies of bacteria or derived from the epithelial cells and secretions of the intestine.

## CHAPTER XVII

### BALANCE-SHEET METHOD OF METABOLISM

Having traced the food substances to their entry into the body in the form of monosaccharides, amino acids, fatty acids and glycerol, and knowing the end products that are excreted from the body it is necessary to compare the two groups of substances. This comparison is done by the balance-sheet method in which the various items are put down with their equivalent energy values, and the whole balanced like a commercial balance-sheet. A positive balance should correspond to a gain in weight and a negative balance to a loss in weight.

The methods used for measuring the various quantities must be described first. The amounts of nitrogen, carbon and hydrogen in the food and excreta are measured by the methods usual in organic chemistry.

**NITROGEN ESTIMATION.** The amount of nitrogen in substances of physiological importance is usually estimated by Kjeldahl's method. This consists in heating the substance with concentrated sulphuric acid, frequently in the presence of a catalyst, until all the carbon has been converted into carbon dioxide. The nitrogen is by this means converted into ammonia which combines with the sulphuric acid to form ammonium sulphate.

The amount of ammonia may be estimated colorimetrically by Nessler's reagent or by distillation. For the latter the solution is rendered alkaline and the ammonia driven off by heating or by a current of air. The ammonia is collected in standard acid and the amount of standard acid neutralized is a measure of the amount of ammonia. One cubic centimetre of a solution of decinormal acid is neutralized by 0.0017 gm. ammonia, which contains 0.0014 gm. nitrogen. Proteins on the average contain 16 per cent. of nitrogen, therefore the amount of nitrogen multiplied by 6.25 is often taken as an indication of the amount of protein corresponding to the amount of nitrogen found ( $6.25 \times 16 = 100$ ).

**CARBON AND HYDROGEN ESTIMATION.** Carbon may be estimated in solution by oxidizing the solution with a strong oxidizing mixture and by collecting the carbon dioxide given off. The more general method is to combust the dry material in a furnace and collect the

water and carbon dioxide formed from which the amount of hydrogen and carbon in the compound can be determined.

### Energy Value of Foods and Excreta

The energy values are measured by burning the substances in the presence of oxygen. A weighed quantity of the substance is placed in a closed vessel full of oxygen. This vessel is immersed in a large volume of water and the substance ignited by a wire heated red hot by an electric current. The heat set free is absorbed by the water. The water equivalent of the calorimeter plus the volume of water both multiplied by the rise of temperature gives the number of calories due to the combustion. The small amount of heat due to the electric ignition apparatus must be subtracted from the gross heat produced. The net heat value divided by the weight of substance burnt gives the heat value per gram. In this way it is possible to measure the heat values of the food and excreta.

### THE DEBIT SIDE OF THE BALANCE-SHEET

The debit side of the balance-sheet is the amount of food material taken in. The amounts of nitrogen, carbon, hydrogen, and the heat value of the food can all be entered on this side of the balance-sheet.

### THE CREDIT SIDE OF THE BALANCE-SHEET

This is a much more complicated matter as we have to trace the various constituents as well as the energy due to their combustion.

#### Indirect Calorimetry

*Fæces.* The analysis of fæces gives the amounts of nitrogen, carbon and hydrogen excreted by or not absorbed from the bowel. This accounts for some of the material and in so far as there are incompletely oxidized substances present a certain amount of the energy value will be lost by the fæces. The values for the food minus the values for the fæces may be looked upon as the net income of the body.

*Urine.* Analysis of urine gives the amounts of nitrogen, carbon and hydrogen excreted from the kidneys. The combustion values of such substances as urea, uric acid, etc., must be represented as part of the expenditure by the body.

*Expired Air.* A large amount of the carbon of the food is represented by the carbon dioxide of the expired air. The water vapour accounts for some of the hydrogen of the food substances. The measurement of the volume of expired air and an analysis of its composition give the data from which to calculate the amount of carbon dioxide and water vapour lost by the breath and the amount

of oxygen absorbed by the lungs. Except for small losses by sweat or by desquamation from the skin the above represent the output of materials from the body.

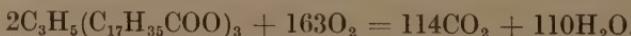
**Respiratory Quotient.** From the figures for urine, faeces and expired air it is possible to calculate the quantities and energy values of the substances actually burned in the body.

Starting with the amount of nitrogen in the urine the amount of protein decomposed is found by multiplying by 6.25 (see p. 208). Knowing the amount of protein and the incompletely oxidized substances formed from it, it is possible to calculate the amount of carbon dioxide produced and the amount of oxygen used during the combustion of protein. Each gram of nitrogen in the urine corresponds to 8.741 gms. or 5.923 litres of oxygen and 9.347 gms. or 4.754 litres of carbon dioxide for the oxidation of protein. If we subtract the amounts of oxygen and carbon dioxide required for the oxidation of protein from the total quantities of oxygen and carbon dioxide as measured by analysis of the expired air, we have left the quantities of oxygen and carbon dioxide which correspond to the oxidation of carbohydrates and of fat.

If carbohydrates are burned there is sufficient oxygen in them to convert all the hydrogen present into water; they require only enough oxygen to oxidize the carbon to carbon dioxide. From the equation  $C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$  we see that the volume of carbon dioxide given off is equal to the volume of oxygen taken in.

The ratio  $\frac{\text{volume of carbon dioxide given off}}{\text{volume of oxygen absorbed}}$  is called the respiratory quotient. In the case of carbohydrates as shown above this ratio equals unity.

During the oxidation of fat part of the oxygen is required to unite with hydrogen to form water, hence the volume of carbon dioxide given off is always less than the volume of oxygen absorbed. Thus the oxidation of tristearin is represented by



From the above equation the respiratory quotient is seen to be  $\frac{114}{163} = 0.70$ .

The respiratory quotient for fat is 0.70 and for protein 0.80. In the latter case in addition to hydrogen other elements such as sulphur combine with oxygen without any corresponding liberation of carbon dioxide.

*Calculation of the Relative Amounts of Carbohydrate and of Fat Oxidized.* The amounts of oxygen and carbon dioxide as measured

after correction for the amount of protein catabolized give a respiratory quotient the value of which will depend upon the relative amounts of non-nitrogenous substances oxidized, i.e. on the relative amounts of carbohydrate and of fat oxidized. It is easy to calculate the relative amounts of carbohydrate and of fat oxidized when the respiratory quotient is known. The following table gives the amounts of these substances oxidized for each litre of oxygen used.

TABLE XXIV (KROGH)

*Per one litre of oxygen.*

| <i>R. Q.</i> | <i>Glycogen catabolized.<br/>(gms.).</i> | <i>Fat catabolized.<br/>(gms.).</i> | <i>Heat Produced.<br/>(C.).</i> |
|--------------|--|-------------------------------------|---------------------------------|
| 0.71         | 0.0000                                   | 0.5027                              | 4.795                           |
| 0.75         | 0.1543                                   | 0.4384                              | 4.829                           |
| 0.80         | 0.3650                                   | 0.3507                              | 4.875                           |
| 0.85         | 0.5756                                   | 0.2630                              | 4.921                           |
| 0.90         | 0.7861                                   | 0.1753                              | 4.967                           |
| 0.95         | 0.9966                                   | 0.0877                              | 5.012                           |
| 1.00         | 1.2071                                   | 0.0000                              | 5.058                           |

The heat produced by the oxidation of the various food substances has been measured by the bomb calorimeter. In the case of carbohydrates and of fats the heat of combustion is the same as that measured by the bomb calorimeter, but in the body proteins yield a smaller quantity of heat energy. The reason for the discrepancy is that protein is not completely oxidized in the body, for the nitrogen is excreted largely in the form of urea. The weight of urea is about one-third of that of the protein from which it is formed. Other losses occur such as lack of complete absorption from the alimentary canal.

TABLE XXV  
HEAT VALUES AND RESPIRATORY QUOTIENTS

|              |   | C.<br><i>in vitro</i><br>per gram. | R.Q. |
|--------------|---|------------------------------------|------|
| Carbohydrate | . | 4.1                                | 1.0  |
| Fat          | . | 9.3                                | 0.7  |
| Protein      | . | 4.1 <sup>1</sup>                   | 0.8  |

<sup>1</sup> The value for protein in the bomb calorimeter is about 5.7.

Having determined the quantities of material metabolized by the nitrogen determination and by analyses of respired air, the various quantities are multiplied by the heat values given in Table XXV. The results are added together to give the energy liberated by oxidation in the body. If more food substances are taken in than are oxidized the body will gain in weight and the converse is also true.

The results obtained by this method agree with those given by direct measurements of the heat lost from the body.

### Direct Calorimetry

This consists in a direct measurement of the total energy output. All the quantities are expressed as heat units. The results of such measurements agree with the energy expenditure as calculated by the indirect method. The indirect method requires less expensive apparatus, hence it is more frequently used. As the comparison of the two methods is so important the fundamental observations have been made by an apparatus which combines both methods, called a respiration calorimeter. This consists of a heat-insulated box or room. The heat insulation is accomplished by an air space, the two walls of which are kept at practically the same temperature. If the two walls are at the same temperature no gain or loss of heat can occur by conduction, radiation, or convection. The inner wall is made of copper and the outer of zinc. There are really two boxes, the smaller one standing inside the larger and separated from it on all sides by an air space. The outer wall (zinc) is maintained at the same temperature as the inner by electrical heating apparatus and lead pipes which can carry a current of cool water. If the inner chamber becomes warmer than the outer wall the outer wall is warmed by the electrical heating apparatus and the cold water is turned off. If the inner chamber is cooler the electric heating is turned off and the cool water started. By varying the electric current and water flow the outer wall can be regulated so as to remain practically at the same temperature as the inner wall.

In order to find out any difference in temperature between the two walls the space is bridged by thermocouples (Fig. 110, E, E). By means of a delicate galvanometer any slight difference in temperature of the two walls can be detected. The walls are divided into sections so that each area can be regulated independently, as slight local differences of temperature might upset the heat insulation. Outside the zinc box are several layers of wood, fibre, etc., to protect the zinc from irregular fluctuations of temperature due to draughts. If all the heat produced is kept inside the calorimeter the temperature would rise indefinitely, but an absorbing system is used so that the calorimeter can be kept almost at a uniform temperature. The heat is absorbed by water circulating through a copper tube with copper flanges. The copper flanges expose a large surface for heat absorption and copper is a good heat conductor. If the weight of water flowing through the calorimeter is known and the difference in temperature between the water entering and leaving the heat absorber is also known the total amount of heat produced in the chamber can be calculated. If any external work done in the calorimeter is converted into heat, e.g. by friction, this heat value is included in the measurement of heat.

The respiration apparatus is connected to the calorimeter in such a way that the air enters and leaves at the same temperature, thus preventing any gain or loss of heat by cooling or warming of the air current. This is arranged by having one air current pass through a container inside the other.

*Measurement of Gases.* The outgoing air is first dried by passing it over concentrated sulphuric acid. The dried air is then passed over alkali to absorb carbon dioxide. It is dried again to prevent loss of moisture from the absorber for carbon dioxide. The reaction whereby carbon dioxide is absorbed sets free water

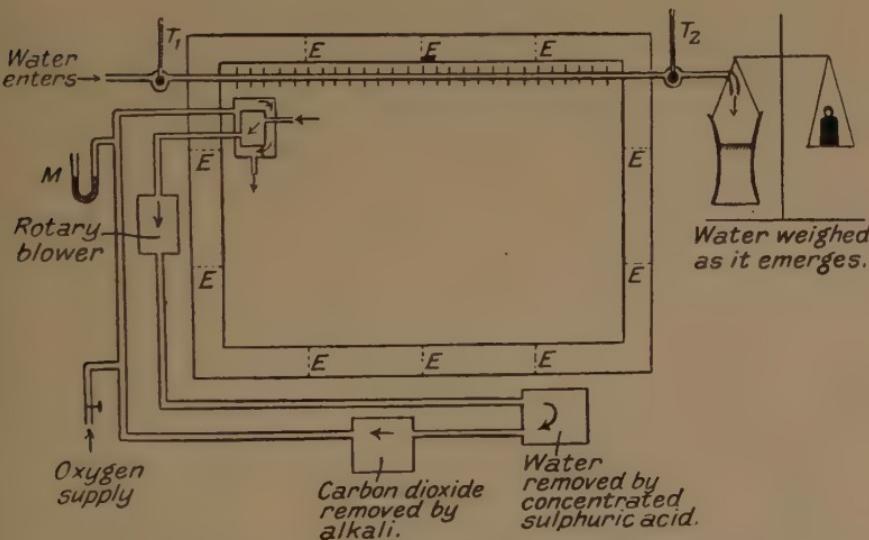
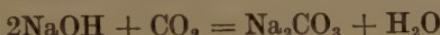


FIG. 110.—Atwater-Benedict Respiration Calorimeter.

A double wall surrounds the respiration chamber. As the two walls are kept at the same temperature no heat can be lost. For description of experimental procedure see text.

The gain in weight of the absorber for carbon dioxide and for redrying the air is a measure of the weight of the carbon dioxide in the air current.

The volume of the air decreases because oxygen is removed by the subject of the experiment. Depending on the value of the respiratory quotient more or less compensation occurs because of the carbon dioxide added to the air. When the carbon dioxide is removed the volume left is less by the amount of oxygen absorbed. A manometer of some sort is used to indicate the decrease in pressure. Oxygen is added from time to time to keep the total volume at the pressure at which the experiment was started. By measuring the volume of oxygen admitted or by noting the decrease in weight of an oxygen cylinder from which the gas is run in, the amount of

oxygen absorbed is determined. During the experiment the water removed from the chamber by the air current is determined by measuring the increase in weight of the first absorbing vessel, containing sulphuric acid. The gain in weight represents a loss of heat as the water must have evaporated in the chamber : the air being dry when it enters from the absorbing system. Multiplying the gain in weight in grams by 0·540 gives the amount of heat in large calories, which must be added to that measured in the calorimeter to obtain the total heat produced in the calorimeter.

At the end of the experiment corrections must be made for any change of temperature in the calorimeter and for any changes in composition of the gases in the calorimeter.

*Measurement of External Work.* If the amount of external work is known the efficiency with which that work is carried out can be calculated. The heat value of the work is absorbed as described above. Measurement of work can be carried out in various ways. If the subject rides a bicycle the work done can be calculated from the number of revolutions of the wheel and the resistance to turning. The force exerted is measured by the difference in tension at two ends of a friction strip running round the back wheel.

The work done is given by the equation

$$\text{Work done} = (t_1 - t_2) nc$$

where  $t_1$  and  $t_2$  are the tensions at the two ends of the friction strip,  $n$  = the number of revolutions and  $c$  = the circumference of the wheel in metres.

The wheel might be used to generate electricity and by measuring the quantity of electricity produced the equivalent work can be determined.

Comparison of direct and indirect calorimetry by means of the respiration calorimeter shows that within the limits of the experimental errors both methods give the same results.

In an experiment in which the diet consisted of protein 100·4 gms., fat 69·1 gms., and carbohydrate 601·0 gms. and the amount of water taken in the form of drink and contained in the prepared food was 2,752 gms., Atwater obtained the following analytical figures. The energy value of this diet is 3,715 C.

TABLE XXVI  
BALANCE OF MATERIALS (DAILY AVERAGE)

|                  | <i>Income.</i> | <i>In faeces</i> | <i>In urine</i> | <i>In expired air.</i> | <i>Expenditure.</i> | <i>Gain or loss.</i> |
|------------------|----------------|------------------|-----------------|------------------------|---------------------|----------------------|
|                  | gms.           | gms.             | gms.            | gms.                   |                     | gms.                 |
| Nitrogen . . . . | 16·8           | 1·6              | 16·9            | —                      | —                   | 1·7                  |
| Carbon . . . .   | 366·3          | 11·7             | 12·8            | 451·5                  | —                   | 109·7                |
| Hydrogen . . . . | 54·0           | 1·6              | 3·2             | —                      | +                   | 49·2                 |
| Water . . . .    | 2,752·0        | 79·3             | 934·4           | 2,672·4                | —                   | 934·1                |

The loss of 934.1 gms. water is equivalent to a loss of 103.8 gms. hydrogen, therefore the net loss of hydrogen becomes (103.8—49.2) 54.6 gms. instead of a gain of 49.2 gms.

The loss from the body corresponded to

|                   | <i>gms.</i> | <i>Nitrogen.<br/>gms.</i> | <i>Carbon.<br/>gms.</i> | <i>Hydrogen.<br/>gms.</i> | <i>Energy.<br/>C.</i> |
|-------------------|-------------|---------------------------|-------------------------|---------------------------|-----------------------|
| Protein . . . . . | 10.8        | 1.7                       | 5.7                     | 0.7                       | 61                    |
| Fat . . . . .     | 136.7       | —                         | 104.0                   | 16.1                      | 1,304                 |
| Water . . . . .   | 339.8       | —                         | —                       | 37.8                      | —                     |
| Total . . . . .   | 487.3       | 1.7                       | 109.7                   | 54.6                      | 1,365                 |

TABLE XXVII

## BALANCE OF ENERGY—DAILY AVERAGE (ATWATER)

| <i>Energy Expended.</i>  | <i>C.</i> | <i>Accounted for.</i>  | <i>C.</i> |
|--------------------------|-----------|--|-----------|
| Food . . . . .           | 3,715     | Warming of ingesta and rise<br>in temperature of calorimeter . . . . . | 28.7      |
| Body substance . . . . . | 1,365     | Evaporation . . . . .  | 731.7     |
|                          |           | External work . . . . .  | 505.8     |
|                          |           | Radiation, etc. . . . .  | 3,497.9   |
|                          |           | Fæces . . . . .  | 126.0     |
|                          |           | Urine . . . . .  | 133.0     |
|                          |           | Balance . . . . .  | 56.9      |
| Total . . . . .          | 5,080     | Total . . . . .  | 5,080.0   |

The amount of energy unaccounted for, namely 56.9 large calories amounts to less than 1.2 per cent. of the total energy exchange. This is a fairly close agreement when one considers the large number of analyses that have to be made in the course of the experiment.

*Benedict Respiration Apparatus.* For many purposes much simpler apparatus is sufficient. The metabolism may be measured by a circulatory system such as that illustrated in connection with the respiration calorimeter.

If the tubes entering and leaving the calorimeter are united by a T piece a closed system results. By breathing through the limb of the T the respired gases pass through the absorbers and come back to be used again. The analyses are carried out by weighing as described above.

*Douglas Bag Method.* This method consists in breathing through valves. The composition of the inspired air is known, hence one only needs to measure the volume of the expired air and to analyze it. The decrease in oxygen and increase in carbon dioxide per hundred cubic centimetres multiplied by the total volume gives the quantities of oxygen taken in and of carbon dioxide given out.

The subject breathes through a face-piece with valves. The expired air escapes through the three-way tap. The experimenter

turns the tap through ninety degrees, after which the expired air passes into the large bag.

After the end of the experimental period the tap is turned back so that no more air enters the bag. The time of collection must be noted. Samples of the expired air are taken for analysis, and the remaining volume in the bag is measured by a gasometer or a meter. The total volume must be that measured plus the volume of the samples taken for analysis. A gasometer may be used instead of the bag for a respiration experiment.

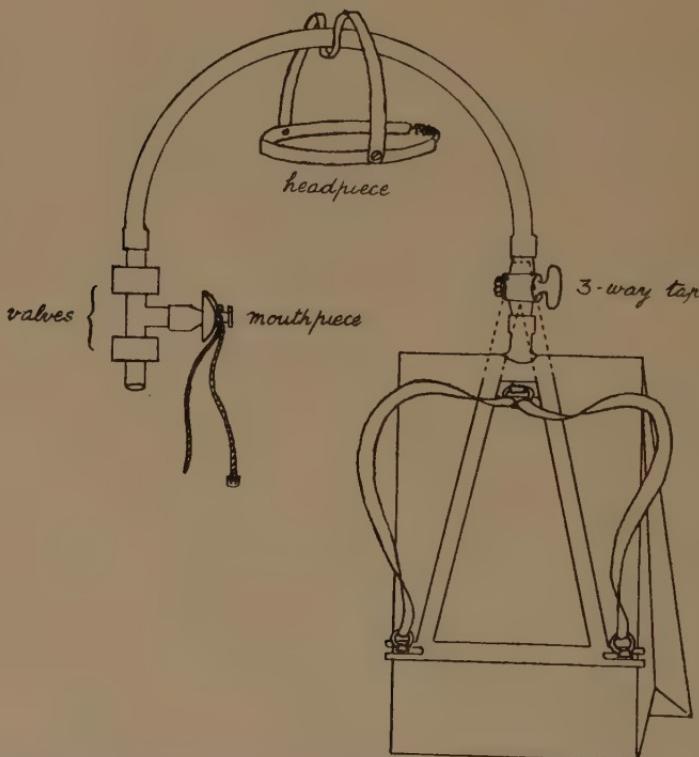


FIG. 111.—Apparatus used for Determining the Total Respiratory Change in Man (C. G. Douglas).  
(For description see text.)

*Haldane's Gas Analysis Apparatus.* The analysis of the gas consists in measuring the diminution in volume when the carbon dioxide is absorbed by alkali, and the further decrease when the oxygen is absorbed by alkaline pyrogallol. The decrease in volume in each case divided by the original volume taken for analysis and multiplied by one hundred gives the percentages of carbon dioxide and oxygen respectively in the expired air. By subtracting the

percentage of oxygen in the expired air from 20·96 the decrease in oxygen can be determined. Correction may be made for the decrease in total volume due to the fact that the respiratory quotient is less than one.

Haldane's apparatus consists of two pipettes, one for absorption of carbon dioxide and the other for absorption of oxygen. The gas burette A, is surrounded by a water bath. In this water bath is an identical tube, N, full of air. This second burette is to compensate for any change in temperature which may occur in the water bath. If the bath becomes warmer the gas expands. This expansion forces down the liquid in the side tube to the alkali pipette E. The reservoir S is raised until the level is forced back to the original mark M. As the volume of gas is always measured to the mark R of the alkali pipette, the gas in the burette will be under the same pressure as that in the compensation tube. This automatically compensates for all differences due to changes in temperature and barometric pressure.

The procedure is to obtain the sample of expired air in the burette A. Measure the volume when the level in the pipette is at R, and with the level of the mercury in B at the same level as the mercury in A. Pass the gas into and out of E until all the carbon dioxide is absorbed. Measure the volume. Turn stopcock so that gas can now be passed into F until all

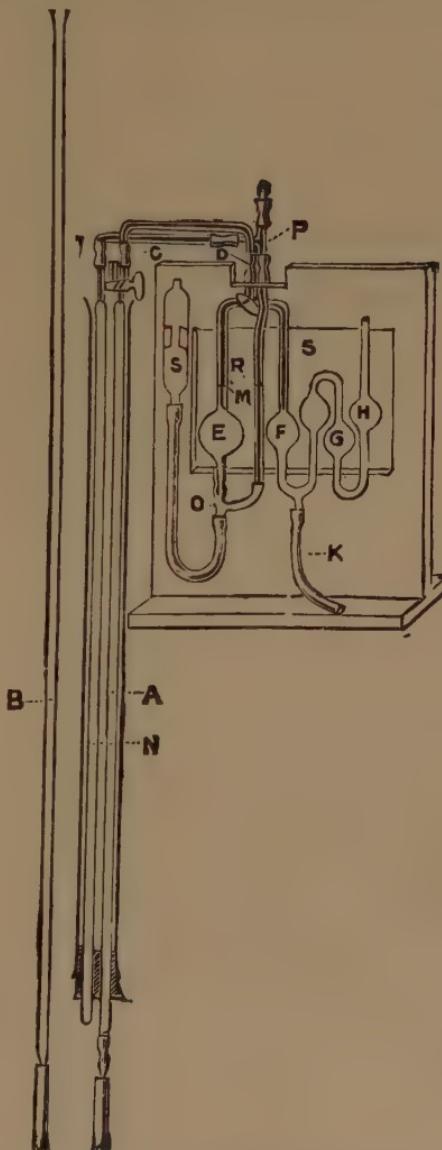


FIG. 112.—Haldane's Gas Analysis Apparatus.

(For description see text.)

the oxygen is absorbed. Withdraw gas until pyrogallol is at its original level. Connect burette with E and measure volume when the level of the liquid is at R as before.

*Example*

| Volume of<br>gas taken. | Volume after absorption |                           | Decrease     |                               |
|-------------------------|-------------------------|---------------------------|--------------|-------------------------------|
|                         | by alkali               | by alkaline<br>pyrogallol | after alkali | after alkaline<br>pyrogallol. |
| 15.5                    | 14.8                    | 12.6                      | 0.7          | 2.2                           |

$$\therefore \text{percentage of carbon dioxide} = (0.7 \times 100)/15.5 = 4.5$$

$$\text{and percentage of oxygen} = (2.2 \times 100)/15.5 = 14.2$$

## CHAPTER XVIII

### CHEMISTRY OF BLOOD

In earlier chapters we have described the nature of the substances taken into the body and the products which are excreted as a result of their metabolism. We have also dealt with the balance of energy and materials in the preceding chapter. In Chapters V and VI we saw that all parts of the body are linked together by means of the circulation ; we must now study the chemistry of the circulating medium or blood. As the blood flows through the various parts of the body there is a continuous interchange between the blood and tissues, therefore the blood will alter in chemical constitution as it passes through the various organs. Any chemical substance that passes from one cell to another will be present in the blood, but the amount of some of these may be very small.

The first striking point about blood is that in the body it is fluid, but soon after it escapes from the vessels it sets to a jelly-like mass. This process of coagulation is of fundamental importance because in the absence of coagulation all surgery would be impossible, and we would bleed to death from the smallest wound. Therefore some description of blood coagulation is necessary, although the views advanced to explain the process are not entirely satisfactory.

#### Coagulation of Blood

If blood is collected in a vessel and it is allowed to stand for about two to six minutes it sets to a jelly occupying the same volume as the freshly shed blood. When it has clotted the vessel may be inverted without any of the blood running out. It is this clotting which closes wounds in blood-vessels. After standing for some time the red clot shrinks and a clear yellow fluid escapes which is called serum. The times taken for these stages of coagulation vary with the conditions, such as the temperature, presence of salts, etc. By altering the conditions the process may be studied in detail.

If the coagulation is allowed to take place on a glass microscope slide it will be seen that the blood consists of solid particles, corpuscles, in a liquid called plasma. When the blood clots, fine threads are formed and these form a network entangling the cor-

puscles. It is the interlacing of these threads which gives the rigidity to the blood clot. After the threads are formed they commence to shrink. By their shrinking they squeeze out the liquid portion and retain the corpuscles entangled. The material of which the threads are formed is known as fibrin. The serum differs from the original plasma in that it does not clot, and some substance has been removed from it which gives rise to the fibrin.

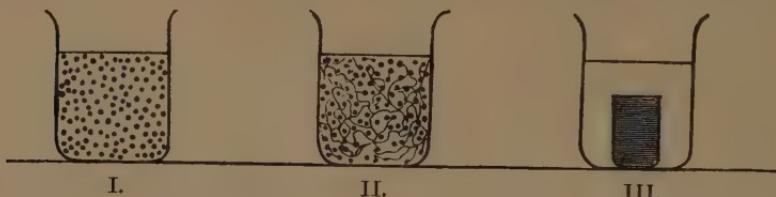


FIG. 113.—Diagram to Illustrate the Process of Coagulation.

I. Fresh  
(corpuscles and  
plasma)

II. Coagulating  
(formation of  
fibrin)

III. Coagulated  
(clot and  
serum)

(After Waller in *Human Physiology*, Longmans, Green & Co.)  
Plasma minus fibrinogen equals serum. Corpuscles plus fibrin equal clot.

If shed blood is kept stirred it does not set, but the process of clotting gives rise to fibrin which becomes entangled on the stirrer in the form of a stringy mass. By this means we are able to obtain the corpuscles suspended in serum and study them without being troubled by the blood setting to a clot. The process of coagulation can be retarded or hastened by various procedures.



FIG. 114.—Network of Fibrin, shown after washing away the Corpuscles from a Preparation of Blood that has been allowed to Clot; many of the Filaments radiate from small Clumps of Blood Platelets.

(From Schafer's *Essentials of Histology*: Longmans, Green & Co.)

prevented or delayed. If paraffined vessels are used coagulation may be delayed for some time. On the other hand, stirring the blood with wires or shaking it with glass beads accelerates the coagulation. It is the increased surface which is of importance in these processes. The coagulation occurs in relation to the surface of foreign bodies.

1. *Effect of Temperature.* Cooling blood slows coagulation, whilst keeping it warm at 40° C. accelerates the process.

2. *Effect of Calcium Salts.* Removal of calcium by a soluble oxalate prevents coagulation. By the addition of calcium salts the process of coagulation is restarted. Citrates act by removing calcium ions as they form a non-ionizing calcium salt.

3. *Effect of Contact with Foreign Bodies.* By preventing blood from coming into contact with foreign bodies coagulation is pre-

As mentioned above the fibrin forms on the stirrer and the blood remains fluid.

4. *Effect of Preservation of Cells.* In Fig. 114 it is shown that the fibrin network radiates from centres where there are remains of cells. The process of coagulation is accompanied by the disintegration of certain cells. The effect of contact with foreign bodies is possibly to promote destruction of these cells. Sodium fluoride is said to inhibit coagulation by preventing the destruction of these cells.

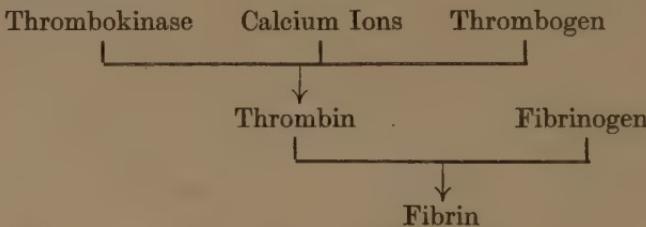
5. *Effect of Extracts from Various Sources.* Extract of leech heads prevents coagulation of blood. On the other hand the venom of *Echis carinatus* accelerates blood coagulation.

6. *Effect of Excess of Neutral Salt.* Excess of neutral salts such as magnesium sulphate or sodium sulphate stops coagulation.

7. *Effect of Peptone.* When peptone is injected into the blood it is said to prevent coagulation. Various explanations have been advanced for this phenomenon. Based on the fact that peptone added to shed blood does not delay coagulation it has been suggested that the peptone causes the liver to secrete an antibody (anti-thrombin). Wooldridge, however, has shown that the peptone does not exert its action through the liver as the peptone effect is linked with the carbon dioxide content of the blood. If carbon dioxide is passed through peptone plasma, it coagulates.

The process of coagulation has been studied by many different observers, but no complete explanation is possible. At one time it was claimed that it was due to stagnation of the blood and that blood did not coagulate in the blood-vessels because it was moving. This view was disproved by the simple expedient of tying the jugular vein of a horse. If the vessel was carefully tied the portion tied off could be removed from the body and coagulation did not occur even if it were kept until the blood putrified. It seems probable that this experiment is explained by the fact that contact with foreign bodies causes coagulation. Blood does not come into contact with the blood-vessel. If water is run over the inner surface of a cut blood-vessel it does not wet the surface. This is exactly similar to the beaker coated with paraffin wax in which blood does not coagulate nor does it wet the surface. If blood has been prevented from coagulation by the addition of an oxalate the corpuscles can be separated by centrifugation. The clear plasma so obtained contains a protein, called fibrinogen, which can be precipitated from the plasma by half-saturation with sodium chloride. It coagulates at a temperature of 56° C. Fibrinogen will clot under appropriate conditions. Sometimes the mere addition of calcium salts will cause this coagulation. Thin threads of fibrin form as in the coagulation of whole blood. Something else besides fibrinogen

and calcium is necessary for coagulation. Birds' blood contains fibrinogen and calcium, but it does not clot if collected through a glass cannula. If it is allowed to come into contact with the tissues it clots : a tissue extract is necessary. In mammalian blood the necessary constituents may be carried down together when fibrinogen is precipitated as the fibrinogen may coagulate on the addition of calcium salts to its solution. We can further show that clotting may occur in the presence of an oxalate, therefore in the absence of calcium. The addition of an extract of fibrin to oxalated blood causes the latter to coagulate. The amount of fibrin formed is said to be proportional to the amount of fibrin extract added, therefore the substance which causes fibrin formation probably forms part of the product of the reaction (fibrin). It is believed that calcium is necessary to produce thrombin ; it is produced from a mother substance thrombogen and a tissue extract thrombokinase. This view, originated by Morawitz, can be shown diagrammatically as follows :



Fibrinogen is contained in the circulating blood and is probably accompanied by thrombogen as they seem to occur together when fibrinogen is precipitated by sodium chloride. Calcium is also present in circulating blood. Thrombokinase is required to start the process, and it can be obtained from tissue cells or from the breakdown of certain white blood corpuscles or from platelets. Thrombokinase may be a mixture of a lipoid with a protein (Mills).

In the plugging of a wound in arthropoda Tait has shown that part of the arrest of haemorrhage is due to the adhesion of white blood corpuscles to the cut margin. Some of these cells break up and form the starting-point for a fibrin network. Probably something of the same sort happens in mammalian blood.

On injection of various substances into the blood stream it has been found that intravascular clotting occurs. These substances contain thrombin or thrombokinase. If they are injected slowly coagulation takes place slowly so that fibrinogen is converted into fibrin without occluding the vessels (cf. stirred blood). Such blood is known as negative-phase blood because it will not clot when shed and it contains no fibrinogen.

Other substances possess the power of preventing the action of

thrombin or thrombokinase. These are regarded as antiferments and are called antithrombins and antithrombokinases respectively.

A somewhat simpler view is advanced by Pickering, namely, that coagulation of blood is due to the gelation of a colloid. The various substances that affect coagulation do so by acting upon the colloidal material of the blood. Contact with foreign bodies may be compared with the precipitation of proteins and saponin on a water-air surface. Calcium salts affect the colloidal condition of the fibrinogen. The schema given above showing the relation of various assumed substances to the process of coagulation is merely a means of linking to the process of coagulation the various experimental methods of producing or retarding it. Fibrinogen and calcium ions can be shown to be present in blood : fibrin is the result of gelation of the fibrinogen. Thrombokinase, thrombogen and thrombin are names used to represent the fact that it requires the interaction of several constituents to initiate coagulation. There is no doubt that coagulation is an irreversible gelation of a colloid, but we must know more about the means whereby the gelation is hastened or retarded.

By preventing coagulation it is possible to separate blood plasma from corpuscles. This is possible because the specific gravity of the corpuscles is greater than that of plasma ; therefore on standing, or more rapidly on centrifugalizing, the corpuscles settle to the bottom of the containing vessel.

The specific gravity of blood can be measured by the usual methods of weighing a known volume or by using a calibrated float, but for small quantities the method of Roy is used. This consists in delivering drops of blood into solutions of known specific gravity. The blood can be seen by its red colour. If the blood rises, its specific gravity is less than the solution, if it sinks the specific gravity is greater ; if it does neither the specific gravity is the same as that of the solution. In order to prevent the blood from being affected by the kinetic energy due to its flowing down the tube, the capillary is bent so that the blood flows out horizontally. The observation should be made immediately the blood enters the solution to minimize the effect of osmotic changes between the blood and the solution.

As standard solutions mixtures of chloroform and benzol, or solutions of glycerol in water, containing mercuric chloride as a preservative, may be used. The specific gravities of the standard solutions are measured by the usual methods.

TABLE XXVIII

|                       | <i>Specific Gravity.</i> |
|-----------------------|--------------------------|
| Whole blood . . . . . | 1055-1062                |
| Plasma . . . . .      | 1026-1029                |
| Corpuscles . . . . .  | 1080-1085                |

The weight of an equal volume of water is considered as 1,000.

When blood is separated into corpuscles and plasma, it is found that approximately sixty to sixty-five parts are plasma and thirty-five to forty are corpuscles. The corpuscles are found to consist of coloured and colourless ones of which the former predominate in the proportion of about 500 : 1.

The red corpuscles in mammals are not true cells as they do not possess a nucleus. The composition of serum and of red blood corpuscles is given in the following table :

TABLE XXIX  
ANALYSIS OF HORSE'S BLOOD (ABDERHALDEN)

| <i>Constituent.</i>                    | <i>Serum.</i>  | <i>Corpuscles.</i> |
|--|----------------|--------------------|
|  | 90.2 per cent. | 61.3 per cent.     |
| Water . . . . .                        | 90.2           | 61.3               |
| Solids . . . . .                       | 9.79           | 38.7               |
| Proteins (other than hæmoglobin) . . . | 8.42           | 5.7                |
| Hæmoglobin . . . . .                   | 0.00           | 31.5               |
| Sugar . . . . .                        | 0.12           | 0.0                |
| Cholesterol . . . . .                  | 0.03           | 0.04               |
| Lecithin . . . . .                     | 0.17           | 0.40               |
| Fat . . . . .                          | 0.13           | 0.00               |
| Sodium . . . . .                       | 0.44           | 0.00               |
| Potassium . . . . .                    | 0.03           | 0.49               |
| Ferric oxide (from hæmoglobin) . . .   | 0.00           | 0.16               |
| Calcium . . . . .                      | 0.01           | 0.00               |
| Magnesium . . . . .                    | 0.005          | 0.008              |
| Chlorine . . . . .                     | 0.37           | 0.19               |
| Phosphoric acid . . . . .              | 0.03           | 0.33               |

### Blood Plasma

By separating blood into plasma and corpuscles we are able to study these two fractions. In all exchanges between the blood and cells it is the plasma with which the exchange occurs because even any constituent which does pass into the corpuscles must reach them through the plasma.

The plasma is a solution in water of inorganic salts, organic crystalloids and colloids as shown in Table XXVII.

The functions performed by the inorganic salts are to maintain the physico-chemical integrity of the body cells ; and to help to maintain the blood at its normal concentration of hydrogen ions. The former function will be discussed later, but the latter will be given a brief consideration here. There is an excess of fixed base over fixed acids in the plasma. This can be shown by ashing the plasma and measuring the amount of acid necessary to neutralize the ash. Before ashing, the excess of base is largely if not entirely combined with carbon dioxide in the form of sodium bicarbonate. We can measure this amount of carbon dioxide combined with bases by rendering the plasma acid, collecting the carbon dioxide

given off and subtracting the amount of carbon dioxide held in solution in a salt solution at the same temperature and partial pressure of carbon dioxide. The excess of fixed base over the fixed acids of the plasma is called the alkali reserve as it represents the amount of alkali available for neutralizing acid added to blood plasma. A solution containing bicarbonate is well adapted to keeping the reaction near a definite point. The concentration of carbonic acid in the blood depends on the pressure of carbon dioxide in the alveoli of the lungs, which is maintained near a partial pressure of 5·6 per cent. of an atmosphere or about 40 mm. pressure.

If acid is added to blood some of the carbon dioxide is set free, but the excess will escape as the blood passes through the lungs. The concentration of hydrogen ions in a solution containing carbonic acid is determined by the first dissociation of carbonic acid.

$$[\text{H}^+] \times [\text{HCO}_3^-] = K[\text{H}_2\text{CO}_3] \text{ where } K \text{ is } 3\cdot04 \times 10^{-7}$$

In the presence of sodium bicarbonate the concentration of bicarbonate ion will be practically the concentration of the bicarbonate as such a salt in the dilution found in plasma is dissociated to about 80 per cent. Therefore, replacing  $[\text{HCO}_3^-]$  by  $0\cdot8[\text{NaHCO}_3]$ , the formula becomes

$$[\text{H}^+] \times 0\cdot8[\text{NaHCO}_3] = K[\text{H}_2\text{CO}_3] \text{ or } [\text{H}^+] = K \frac{[\text{H}_2\text{CO}_3]}{0\cdot8[\text{NaHCO}_3]}$$

The concentration of bicarbonate in plasma is slightly less than  $3 \times 10^{-2}$  N and the concentration of carbonic acid is that equivalent to a solution in equilibrium with the alveolar air. The presence of other substances introduces complications, but the ratio shown above holds in a solution of bicarbonate. Thus we see that addition of acid does not cause a large change of hydrogen ion concentration but a smaller change due to the alteration of the ratio of dissolved carbonic acid to sodium bicarbonate in the solution.

The organic crystalloids of blood plasma consist of traces of many different substances. Amino acids and glucose absorbed from the intestine passing to the tissues, urea passing from the tissues to the kidneys, and all other substances carried from one part of the body to another are found in the plasma.

TABLE XXX

## APPROXIMATE CONCENTRATIONS OF ORGANIC CRYSTALLOIDS

|                                      |                                    |
|--------------------------------------|------------------------------------|
| Total non-protein Nitrogen . . . . . | 30·0 milligrams per 100 c.c. blood |
| Urea . . . . .                       | 15·0 , , ,                         |
| Uric acid . . . . .                  | 2·0 , , ,                          |
| Creatinine . . . . .                 | 1·5 , , ,                          |
| Creatine . . . . .                   | 4·5 , , ,                          |
| Amino acids . . . . .                | 4·0 , , ,                          |
| Glucose . . . . .                    | 120·0 , , ,                        |

Q

**Proteins.** The colloids of blood plasma consist of proteins. Other substances known to be present may be incorporated with the disperse protein phase. Thus the amount of fat is 0·13 per cent., and such a concentration in salt solution would form an opaque emulsion, but although the blood plasma may be slightly cloudy after a meal rich in fat or when fat is being transferred from one tissue to another, it is usually transparent. The proteins are fibrinogen, serum albumins and serum globulins. The fibrinogen is a special globulin concerned with blood coagulation (see beginning of this chapter); it is precipitated by half-saturation with sodium chloride and coagulates at a temperature of 56° C. The albumins and globulins are characteristic of their groups. The amount of globulin precipitated by dialysis is less than that precipitated by half-saturation with ammonium sulphate; therefore two globulins are said to be present, namely pseudoglobulin precipitated by half-saturation with ammonium sulphate, but not by dialysis, and euglobulin precipitated by half-saturation with ammonium sulphate and by dialysis.

The functions of the albumins and globulins is not very obvious. They are not necessary for the nutrition of the tissues, as glucose, amino-acids and fats are present in the plasma. They may have some influence in maintaining the reaction of the blood because of their amphoteric nature, but it is claimed that at the reactions found in normal blood the proteins do not exert much influence.

Thus one must look to the physical properties of the protein as a possible explanation of their function.

Proteins have a relatively high viscosity, therefore the proteins have an influence in maintaining the blood pressure. The viscosity delays the flow of blood through the small blood-vessels, therefore the blood does not escape too rapidly from the arteries between the heart-beats. The viscosity of plasma is about four times that of water, and whole blood containing corpuscles has a still higher viscosity owing to the friction of the corpuscles.

Proteins have an osmotic pressure. This pressure is low compared to that of the crystalloids of blood, but it is more effective for the following reason. Crystalloids diffuse readily through most membranes, therefore their concentrations become equalized on both sides of the membrane and effective pressure is lacking. The proteins do not readily diffuse, hence their osmotic pressure is effective. The proteins thus retain water in the blood-vessels by opposing any tendency for the water to pass away from the plasma. The osmotic pressure of proteins varies according to the amount of acid or alkali combined with them, but the variations in the inert proteins of plasma are less than in the more reactive proteins of corpuscles and tissue cells.

TABLE XXXI

## FREEZING-POINT AND OSMOTIC PRESSURE OF PLASMA AND PLASMA PROTEINS

|   | Depression of<br>freezing-point. | Pressure<br>(in millimetres of<br>mercury). |
|---|----------------------------------|---|
| Osmotic pressure of plasma . . . . .      | 0·560° C.                        | about 4,040                                 |
| Osmotic pressure of plasma proteins : . . | 0·004° C.                        | about 40                                    |

The proteins may be of use in holding insoluble materials like fat in solution, thus helping their transport in the body.

## Red Blood Corpuscles

The red corpuscles of blood are easily broken up by various agents. Thus if a drop of blood be placed on a slide and covered by a cover glass the corpuscles can be seen under the microscope. If now a drop of distilled water be added to the drop the corpuscles are seen to swell and to lose their colouring matter, leaving a faint ghost-like residue called the *stroma*. On the other hand addition of a strong salt solution causes them to shrink and become irregular in shape: this is called *crenation*. On holding these slides to the light it is seen that the normal blood is opaque whilst that in which the colouring matter has escaped from the corpuscles is transparent. The reason for this difference is that the intact corpuscles reflect light, so that the blood appears opaque and a bright red, whilst the corpuscles after losing their haemoglobin do not reflect light, so that the suspension is transparent and dark-red. For this reason the breaking-up of red corpuscles is known as *haemolysis* or *laking*.

**Hæmolysis** can be brought about in many different ways, such as freezing solid, warming to 60° C., dilution with water, addition of acid or alkali, addition of chloroform, ether or alcohol, action of saponin or bile salts, and by certain animal products. The large number of ways in which haemolysis is produced are sometimes grouped under four headings: Physical, Chemical, Physico-chemical, and Biological.

The physical processes are cold, heat, and shaking; the chemical processes are the action of acid and of alkali, the effect of chloroform, ether and alcohol; the physico-chemical processes are dilution with water, action of saponin and bile salts; whilst the biological processes are due to the action of biological products of unknown composition called *haemolysins*.

In order to understand these processes we must know something of the structure of the red blood corpuscles. As shown in the table on page 224, the corpuscles consist mainly of a red pigment haemoglobin with certain other substances such as proteins and fats. The corpuscle must have some kind of structure, either an enclosing wall or a mesh-like framework, because their shape, which

is that of a bi-concave disc, is impossible in a fluid structure. The surface tension would produce a positive pressure inside at the convex part, of the corpuscle and a negative pressure inside at the concave part, therefore the same fluid would have a positive and negative pressure at the same time, which is absurd.

Hæmalysis may be either the disruption of the structure or the setting free of the hæmoglobin from some association with the framework. Most of the phenomena of hæmalysis are best understood on the assumption that the hæmoglobin is retained in the corpuscle by an enclosing wall or membrane, but it may be that it is contained in a sponge-like network. On freezing corpuscles solid the ice formed in the corpuscles would burst the containing walls just as water pipes are burst by the increase in volume when water is turned into ice. When the corpuscles thaw the hæmoglobin escapes. On warming corpuscles to 60° C. hæmalysis occurs. This is sometimes ascribed to melting of a hypothetical fatty wall, but it is more probably due to the increase in osmotic pressure of hæmoglobin with rise of temperature.



FIG. 115.—Drawings of Red Blood Corpuscles.

*a* = surface view, *b* = profile view, *c* = short rouleau of corpuscles.

Shaking red blood corpuscles with asbestos fibre causes hæmalysis, which may be due to a mere mechanical action on the corpuscles.

The action of acid and alkali is probably due to their action on the proteins of the corpuscle. Both acid and alkali cause a marked increase in the osmotic pressure of hæmoglobin (Roaf), but it is difficult to prove that this increase is the cause of hæmalysis. An alternative view is that acid and alkali saponify lipins in the membrane of the corpuscle, but no experimental proof is forthcoming in support of such an hypothesis.

Chloroform, ether, alcohol, etc., are stated to produce their effect by a solvent action on lipins. In the concentrations which cause hæmalysis these substances would not dissolve lipins, but would themselves be dissolved in the fats. This solution in the fats might have a disruptive effect if it were proved that the integrity of the corpuscle were due to a fatty wall. It must not be forgotten that chloroform and such substances have an action on protein so that they may cause hæmalysis either by an action on lipins, on proteins or on both.

In the preceding paragraphs it has been assumed that the hæmalysis which took place by the action of the various agencies occurred in sodium chloride of osmotic concentration equal to that

of the blood (0·9 per cent.), because mere dilution of sodium chloride will cause haemolysis which is complete when the concentration of salt falls as low as 0·6 per cent. Such dilution should cause a marked difference in osmotic pressure with swelling and rupture of the corpuscle. If the corpuscle is impermeable to sodium chloride the difference in osmotic pressure would be about 1,500 millimetres of mercury after allowing for dilution of the contents of the corpuscle due to its swelling. This is the usual explanation offered for haemolysis by dilution. Although one cannot prove that the corpuscle wall is impermeable it behaves in many ways as if it were. There is evidence that salts can pass into and out of the corpuscle.

Further, many crystalloids act as if the concentrations at which haemolysis occurs were merely a function of the molecular and ionic concentration, i.e. the effect is proportional to their action on the vapour pressure of the solution. This can be explained either by regarding the corpuscle as possessing a wall impermeable to these crystalloids or as a solution of water in a phase which is immiscible with the crystalloid solutions.

On the other hand certain crystalloids do not prevent haemolysis and they behave as if they become equally distributed between corpuscles and surrounding solution. It is customary to say that the corpuscle is permeable to these substances but not to those which prevent haemolysis.

TABLE XXXII

## EFFECT OF VARIOUS SUBSTANCES ON RED BLOOD CORPUSCLES

| <i>Substances which prevent haemolysis.</i> | <i>Substances which do not.</i>       |
|---|---------------------------------------|
| Sodium chloride                             | Ammonium salts                        |
| Potassium nitrate                           | Urea                                  |
| Many other salts                            | Alcohols, aldehydes and ketones, etc. |
| Sugars, etc.                                |                                       |

Amino-acids seem to enter the cells slowly.

Certain other substances, such as bile salts, saponin, etc., produce haemolysis. These substances have a marked effect in decreasing the surface tension at an air—water surface. It is tempting to regard this form of haemolysis as produced by a disrupting effect on the corpuscle structure due to the dispersion of the colloids by a decrease in surface tension. The action of certain animal products such as snake venoms in producing haemolysis may be due to an action on the surface tension. It is, however, interesting as introducing us to the subject of haemolysins. If an animal is injected with red blood corpuscles of another species the serum of the injected animal acquires the property of haemolysing the corpuscles of the species with which it has been injected. Thus we see that several injections of a foreign body produce a reaction

whereby the foreign body is destroyed. This method of producing haemolysins is an example of the production of antibodies (see p. 548).

The chemistry of the haemoglobin contained in red blood corpuscles will be more conveniently described in connection with the chemistry of respiration in the next chapter.

### White or Colourless Corpuscles

The colourless corpuscles can be demonstrated by three methods. (1) Blood can be spread on a slide to form a thin film, and the corpuscles stained in various ways. (2) The blood can be centrifugalized, and the top layer of corpuscles separated from the plasma and from the red corpuscles below : the white corpuscles being mainly with the top layer of corpuscles. (3) The red blood corpuscles may be destroyed by haemolysis and the white corpuscles examined.

The first method distinguishes the white corpuscles because they are nucleated cells which stain in various ways by aniline dyes. The second method separates the white cells because they are of less specific gravity than the red cells, and they settle on top of the layer of red cells, forming what is called the "buffy" coat. The third method shows the colourless corpuscles because they do not break up so readily as the red blood corpuscles.

The appearance and relative numbers of white blood corpuscles is shown in Table XXXIII and in Fig. 116. The functions of these cells will be discussed later.

TABLE XXXIII  
CLASSIFICATION OF WHITE BLOOD CORPUSCLES

|   | Relative Number. | Size in Micra |
|---|------------------|---------------|
| <i>Lymphocytes.</i> Small cells each with a single round nucleus . . . . .  | 20-30 per cent.  | 10-12         |
| <i>Monocytes or Transitional Cells.</i> Large cells with large oval nuclei or with lobed nuclei . . . . .   | 3-6 , ,          | 12-20         |
| <i>Polymorphonuclear Cells.</i> Medium-sized cells the nuclei of which are subdivided into several distinct portions. The protoplasm contains many fine granules which stain with eosin . . . . . | 55-70 , ,        | 9-12          |
| <i>Eosinophiles.</i> These resemble the polymorphonuclear cells, only they contain large granules which stain markedly with eosin, hence they are acidophile granules . . . . .                   | 1-3 , ,          | 12-15         |
| <i>Mast Cells (basophile).</i> These are also like the polymorphonuclear cells, but in these the granules are few in number and stain with basic dyes . . . . .                                   | 0.5 , ,          | 10            |

In order to make a *differential count* of white blood corpuscles a

blood film is made and stained with some suitable stain such as Leishman's stain. The white cells are examined and each one classified into one of the above groups. When several hundred leucocytes have been counted the average number of each kind can be determined.

To count the total number of red or white cells a method of

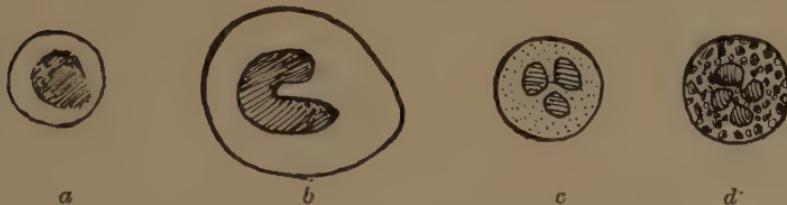


FIG. 116.—Drawings of White Blood Corpuscles.

*a* = small lymphocyte, *b* = large mononuclear, *c* = polymorphonuclear leucocyte, *d* = eosinophil.

dilution is used. A known volume of blood is diluted with a known volume of diluting fluid. After the sample has been thoroughly mixed a drop of the mixture is placed on a special counting slide. The slide has on it a disc ruled in squares of definite area. The disc is mounted so that it is in the centre of a circular hole in a

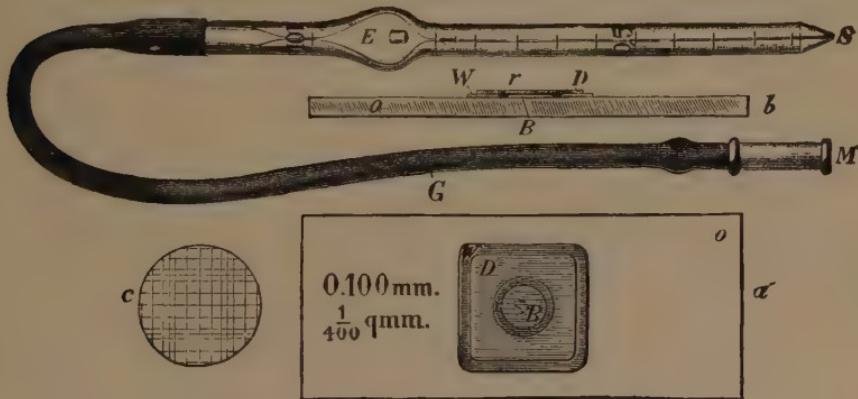


FIG. 117.—Thoma-Zeiss Hæmaeytometer.

*B* = disc ruled in squares shown magnified at *c*, *D* = cover-glass resting on glass square *W* pierced by circular hole, *E* = mixing chamber containing glass bead.

piece of square glass cemented on the same slide. The thickness of the glass square is greater than the disc, so that when a plane cover-glass is placed over the square there is a space of definite thickness over the disc with the ruled squares.

In the case of the Thoma-Zeiss apparatus the volume of blood taken is measured in a glass capillary. This is diluted by sucking

the diluting fluid and the blood into a bulb. In the bulb is a glass bead which on being shaken causes the blood and diluting fluid to mix. In order to count the red blood corpuscles the diluting fluid consists of some fluid which prevents haemolysis, such as 0·9 per cent. sodium chloride. The dilution is about one in a hundred or one in two hundred. The stem of the pipette is graduated so that one can use various lengths of it. The whole stem is one unit and the pipette up to the top of the bulb is one hundred and one units. Therefore the bulb contains one hundred units as the one unit of the stem is filled with the diluting fluid. If one unit of blood is taken the dilution is 1 : 100, but if only half that quantity of blood has been sucked into the stem the dilution will be 1 : 200. After mixing, the fluid in the stem must be got rid of and the stem well washed out by several drops of mixture from the bulb. A minute portion of the mixture is next placed on the disc and a cover-glass placed on the cell, taking care that the drop does not spread beyond the disc into the well between it and the glass square.

The squares each have a side of  $\frac{1}{20}$  mm., therefore the area of each square is  $\frac{1}{400}$  sq. mm. The depth of the cell is  $\frac{1}{10}$  mm., therefore the volume of liquid over each square is  $\frac{1}{4000}$  cu. mm. By counting the number of corpuscles covering a large number of squares the average number per square is determined. The number per square multiplied by 4,000 gives the number per cu. mm., which, multiplied by the dilution, gives the number in the original blood.

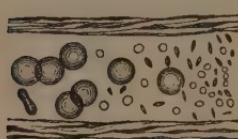


FIG. 118.—Blood Corpuscles and Blood Platelets within a Small Vein (W. Osler).

(From Schafer's *Essentials of Histology*: Longmans, Green & Co.)

$$200 = 5,600,000.$$

The white corpuscles may be counted at the same time if the diluting fluid contains a dye which will stain them, but it is better to destroy the red blood corpuscles by haemolysis. The diluting fluid for this purpose is 0·5 per cent. acetic acid in distilled water tinted with a stain such as methyl violet. The number of white corpuscles is only 1 : 500 red corpuscles, therefore after destroying the red corpuscles a lower dilution may be used. A smaller pipette to give a dilution of one in ten or one in twenty is provided with the apparatus.

The number of white corpuscles is more variable than the number of red corpuscles. There are about six million red corpuscles per cu. mm. in men and about five and a half million in women.

The white corpuscles vary between five and ten thousand per cu. mm.

In addition to the red and white corpuscles one finds in blood small particles known as platelets. These can be seen in a stained specimen of blood. They are reputed to be concerned in blood coagulation: they may set free thrombokinase.

In a later chapter the function of the white corpuscles will be discussed.

## CHAPTER XIX

### CHEMISTRY OF RESPIRATION

The chemistry of respiration consists in the taking in of oxygen and giving off of carbon dioxide with the intermediate steps by which the food materials are oxidized. The oxidation of food materials occurs in the cells of the tissues, whereas the exchange of gases with the atmosphere occurs in a specialized organ, the lung. Therefore respiration can be considered under three headings, namely : (1) external respiration or gas exchange in the lungs ; (2) internal respiration or oxidation in the cells ; and (3) transport of gases in the blood between lungs and other tissues.

#### EXTERNAL RESPIRATION

The mechanics of this process have been described in Chapter IV. The chemical changes can be demonstrated by analysis of the gases of inspired and expired air, or more simply by the following experiment :

Breathe through the T-piece uniting a pair of flasks containing lime water. The two flasks are so arranged that each has a long tube dipping below the surface of the lime water and a short tube opening into the air space above the liquid. The flasks are connected so that the T-piece is connected to the short tube of one and the long tube of the other (see Fig. 38, p. 31). Therefore air is sucked through the long tube of the first flask and blown out through the long tube of the second. The first flask will show a slight precipitate due to the small amount of carbon dioxide in the inspired air, and the second will show a copious precipitate of calcium carbonate because of the greater amount of carbon dioxide in the expired air.

The deficiency of oxygen in the expired air can be demonstrated but not proved by the fact that a candle will be extinguished if it is placed in a vessel containing air obtained at the end of an expiration.

In order to measure the quantities of gases in the air analyses are made by measuring the decrease in volume when the separate gases are absorbed by suitable reagents (see p. 216). In a normal quiet respiration a certain amount of the air breathed in remains in

the larger air tubes and does not reach the air sacs where gas exchange with the blood takes place. During expiration this air is breathed out unaltered save for the addition of water vapour and a rise in temperature. As this portion of the respiratory tract does not take part in the exchange of gases it is called the *dead space*.

Owing to the existence of this dead space the first portion of air breathed out is practically unaltered in composition. As expiration continues the air from the air sacs washes out all the air that has been in the trachea and bronchi. Towards the end of expiration the expired air is practically the same in composition as the air in the alveoli. Between the two extremes the expired air will be intermediate in composition between the inspired air and alveolar air, the relative amounts of the two depending on the amount of mixture that occurs by eddy currents in the air passages. This change in composition of the air in the trachea is represented in Fig. 120, in which the variations in gas pressures in the trachea are shown by continuous lines swinging from the values for inspired air to those for alveolar air.

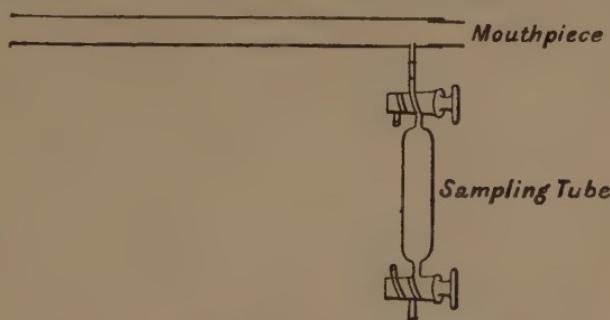
The expired air as collected is a mixture of relatively unaltered air from the dead space and air from the alveoli.

FIG. 119.—Apparatus for Collection of Samples of Alveolar Air (Haldane and Priestley).

A deep expiration is made and the mouthpiece immediately closed by the tongue. A sample of air is drawn off by opening the upper tap of the evacuated sampling tube.

**Alveolar Air.** Haldane and Priestley have devised a method for obtaining alveolar air. This consists in making a deep expiration, with nose closed, down a long tube about 1 inch in diameter. The air from the air spaces forces out all the air in the dead space, and the volume is sufficiently large to wash out all the connecting tubes and leave some relatively undiluted alveolar air in the long tube near the mouth. The mouth end of the tube is closed by the tongue, and a sample of alveolar air is drawn off for analysis near the mouth. As the sample is drawn off fresh air enters the far end of the tube and mixing currents occur. Therefore one must avoid drawing off too large a sample, otherwise it may be contaminated by air which does not represent that contained in the air sacs.

Such a sample is usually considered to represent the composition



of the gas with which the blood is in equilibrium, but it is not improbable that this composition is only an approximation to the true alveolar air. When the volume of the lungs decreases, the alveoli and infundibula decrease so that the gas in them is forced out. The gas in the infundibula will pass out first and afterwards that in the more remote alveoli. The uniformity of composition in the air sacs will depend on the efficiency of mixing, and it is not improbable that the gases in the layer next to the lining wall may be quantitatively different from those in the more central portions. Further, the immense surface of the lung will cause a certain amount of friction, so that there will be a tendency for the surface layer to remain in contact with the alveolar walls. The importance of this will be appreciated when one attempts to explain the exchange of gases between the alveoli and blood. Analysis of the gases shows the following proportions when measured as dry gases at atmospheric pressure :

TABLE XXXIV  
COMPOSITION OF RESPIRED GASES

|                    | Oxygen. | Carbon Dioxide. | Nitrogen. |
|--------------------|---------|-----------------|-----------|
| Inspired Air . . . | 20.96   | 0.04            | 79.0      |
| Expired Air . . .  | 16.40   | 4.1             | 79.5      |
| Alveolar Air . . . | 14.00   | 6.0             | 80.0      |

The change in the percentage of nitrogen is due to a decrease in volume of the air owing to the volume of oxygen absorbed being greater than the volume of carbon dioxide given off.

The volume of tidal air at each quiet respiration is about 500 c.c. : from this figure and the analyses shown in Table XXXIV we can calculate the volume of the dead space. The relative proportions of inspired and alveolar air necessary to produce the percentage of oxygen in expired air multiplied by the volume of the tidal air gives the volume of the dead space. Let  $x$ =volume of the dead space, whence

$$20.96x + 14(500 - x) = 16.4 \times 500 \\ \therefore x = 172 \text{ approximately.}$$

As the dead space does not show wide variations the effective ventilation of the lungs per respiration will increase more rapidly than the relative increase of the depth of respiration, as shown in Table XXXV. Therefore, increase in depth of respiration is an effective way of increasing pulmonary ventilation.

It is probable that the dead space varies in volume, but the degree to which it varies is not yet determined. The bronchioles have muscular walls which by their contraction will alter the volume of the tubes : therefore the amount of air contained in them will change. Excessive contraction of the muscles, as in

TABLE XXXV

| EFFECT OF DEPTH OF RESPIRATION ON PULMONARY VENTILATION |                        |             |                        |
|---|------------------------|-------------|------------------------|
| No.   | Volume of Respiration. | Dead Space. | Effective Ventilation. |
| 1   | 300                    | 172         | 128                    |
| 2   | 400                    | 172         | 228                    |
| 3   | 500                    | 172         | 328                    |
| 4   | 700                    | 172         | 528                    |
| 5   | 900                    | 172         | 728                    |
| 6   | 1,200                  | 172         | 1,028                  |
| Ratio of 1 : 6  | 1 : 4                  |             | 1 : 8                  |

asthma, will interfere with the passage of air in and out of the lungs, and will also change the volume of the dead space.

The passage of gas from the lungs to the blood will depend upon the partial pressures of the two media. In general, the pressure of oxygen in the alveolar air is greater than that in the blood, and the pressure of carbon dioxide in the blood is greater than that in the alveolar air ; therefore gas exchange can take place by diffusion.

Whether diffusion is the sole cause of gas exchange is a matter of opinion. The analysis of alveolar air, as mentioned above, may not give the true composition of the layer of air close to the wall of the alveoli ; thus the differences quoted between the tension of gases in the alveolar air are maximum differences. Further, if gas exchange is merely a matter of diffusion we must be able to show that the differences of pressure are sufficient to cause the amount of gas exchanged to diffuse through the area of lung which is being used for diffusion, i.e. the gradient of pressure (difference of pressure per unit thickness of tissue) must be sufficient to force the gas through unit area at the requisite speed.

During respiration the composition of the alveolar air will vary slightly. About 338 c.c. of fresh air enter the lungs, which contain about 3,000 c.c. This slight difference is shown by the difference in composition of alveolar air obtained at the end of inspiration and at the end of expiration. The slight variations in partial pressure are shown by the dotted lines in Fig. 120.

### Transport of Gases in the Blood

The oxygen absorbed from the lungs is carried to the tissues, and the carbon dioxide is carried from the tissues to the lungs in the blood. We must therefore consider the conditions under which gases can pass into and out of a liquid.

When a liquid is exposed to a gas the gas dissolves until the rate of diffusion out of the liquid equals the rate of diffusion into the liquid. It is therefore a phenomenon depending on the presence of two phases (see Chapter XI). When the gas has dissolved in the surface layer it can be carried to other parts of the liquid by diffusion or by mass movement.

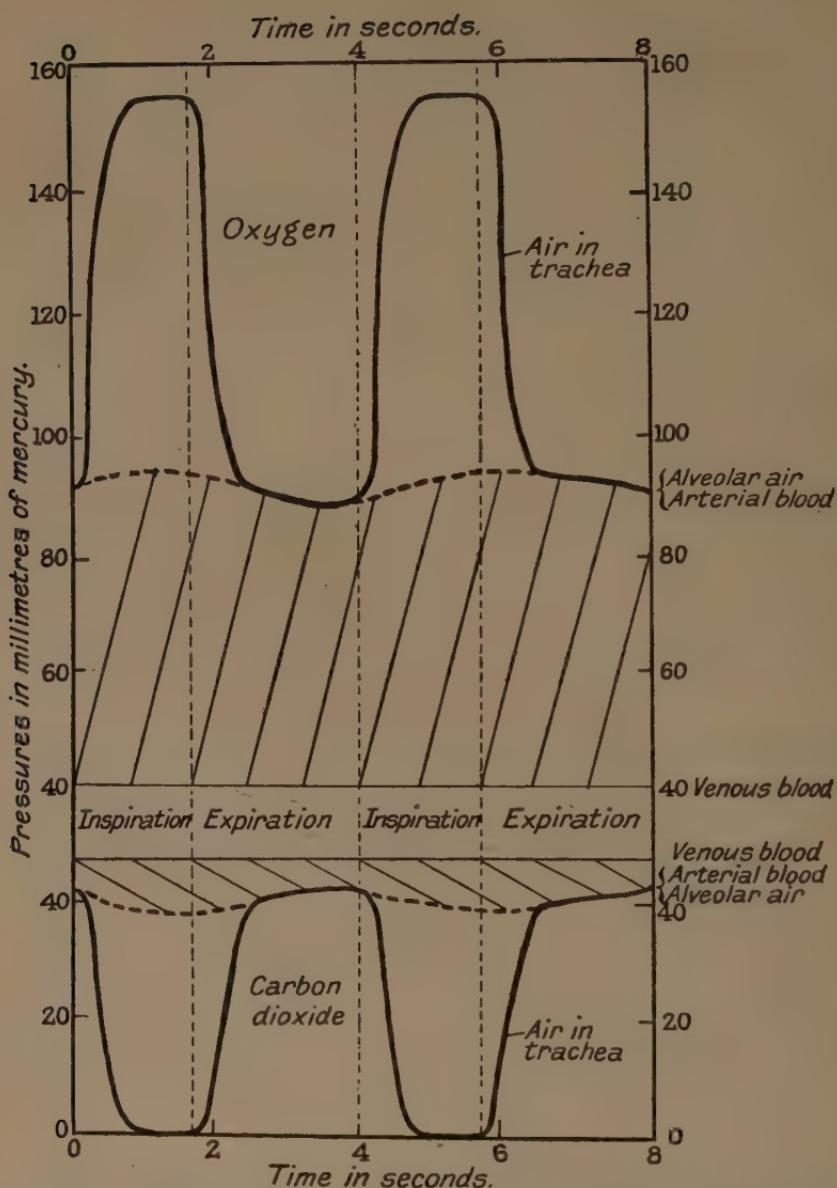


FIG. 120.—Partial Pressures of Oxygen (upper part) and Carbon Dioxide (lower part) in Dead Space (Trachea), Alveolar Air, Arterial Blood and Venous Blood. Two Respirations are shown.

The partial pressures in the dead space change most as they vary from those of atmospheric air to those of alveolar air. The partial pressures in the alveolar air alter slightly owing to the admixture with a small amount of fresh air at each inspiration. The pressures in arterial blood are practically the same as those in alveolar air, and the pressures in venous blood are constant at a level which depends on the activity of the body.

The sloping lines represent the rate at which the partial pressures change in a corpuscle or in the plasma, assuming that it takes one second to pass through the capillaries of the lung. The slower rate of diffusion of oxygen than of carbon dioxide corresponds to the greater difference in partial pressures of oxygen between venous and arterial blood.

When equilibrium has been attained the tendency for the gas to escape is spoken of as its partial pressure. As this pressure balances the pressure of the gas in the space above it we can express it as a percentage strength, and knowing the atmospheric pressure from the percentage strength we can calculate the partial pressure of the gas. The alveolar air contains about 6.0 per cent. of carbon dioxide, and for an atmospheric pressure of dry air of about 720 mm. Hg this is equivalent to about 43 mm. Hg pressure.

If the gas is dissolved in the same molecular condition as it is found in the gaseous phase the amount dissolved is proportional to the partial pressure, i.e. percentage in solution =  $(a \times \text{partial pressure}) \div 7.6$ , where  $a$  = the coefficient of absorption.

The coefficient of absorption,  $a$ , is the volume of gas, measured at 0° C. and 760 mm. Hg pressure, which is dissolved in one volume of the solvent when the partial pressure of that gas equals 760 mm. Hg; therefore the percentage of gas in the solution is determined by multiplying the coefficient of absorption by 100 and by the partial pressure of the gas and dividing the product by 760, i.e. percentage of gas in solution

$$\begin{aligned} &= (a \times 100 \times \text{partial pressure}) \div 760 \\ &= (a \times \text{partial pressure}) \div 7.6. \end{aligned}$$

TABLE XXXVI

SOLUBILITIES OF GASES IN WATER (LANDOLT AND BÖRNSTEIN) AND IN BLOOD (BOHR)

Volumes, at 0° C. and 760 mm. Hg, of gas dissolved in one volume when partial pressure of that gas equals 760 mm. Hg.

| <i>Temperature.</i>                |  | <i>Oxygen.</i> | <i>Carbon Dioxide.</i> | <i>Nitrogen.</i> |
|------------------------------------|--|----------------|------------------------|------------------|
| (a) Water :                        |  |                |                        |                  |
| 0° C. . . . .                      |  | 0.04922        | 1.713                  | 0.02354          |
| 15° C. . . . .                     |  | 0.03459        | 1.019                  | 0.01685          |
| 25° C. . . . .                     |  | 0.02887        | 0.759                  | 0.01434          |
| 35° C. . . . .                     |  | 0.02492        | 0.592                  | 0.01256          |
| (b) Blood at 38° C. . . . .        |  | 0.02200        | 0.511                  | 0.01100          |
| (c) Blood plasma at 38° C. . .     |  | 0.02300        | 0.541                  | 0.01200          |
| (d) Blood corpuscles at 38° C. . . |  | 0.01900        | 0.450                  | 0.01000          |

From Table XXXVI we can calculate the amounts of gas dissolved in blood at different pressures. For instance, with a partial pressure of 40 mm. Hg of carbon dioxide at 38° C., whole blood would contain  $(0.511 \times 40) \div 7.6 = 2.69$  c.c. of carbon dioxide at 0° and 760 mm. Hg pressure. In this way Table XXXVII has been constructed to show the amounts of gases which would be dissolved at various partial pressures.

TABLE XXXVII

AMOUNTS OF GASES IN 100 C.C. OF BLOOD AT 38° C. AND DIFFERENT PARTIAL PRESSURES

| Pressures.            | Oxygen. | Carbon Dioxide. | Nitrogen. |
|-----------------------|---------|-----------------|-----------|
| 10 mm. Hg . . . .     | 0·03    | 0·67            | 0·014     |
| 40 " " " "            | 0·12    | 2·69            | 0·058     |
| 100 " " " "           | 0·29    | 6·72            | 0·145     |
| 150 " " " "           | 0·43    | 10·08           | 0·217     |
| 1 Atmosphere . . . .  | 2·20    | 51·10           | 1·100     |
| 3 Atmospheres . . . . | 6·60    | 153·30          | 3·300     |
| 8½ " " " "            | 18·80   | 434·30          | 9·300     |

NOTE. 40 mm. Hg corresponds to the alveolar pressure of carbon dioxide. 100 mm. Hg corresponds to the alveolar pressure of oxygen. Three atmospheres represents the pressure of nitrogen which might be present in a caisson, and 8½ atmospheres shows the pressure of oxygen that would be necessary to keep in simple solution the volume of oxygen that is present in blood, and that pressure is about 65 times that present in the alveolar air.

The corresponding volume of gases which can be obtained from arterial blood are at 40 mm. Hg pressure of carbon dioxide, 48, and at 100 mm. Hg pressure of oxygen, 18·8. These figures are about 18 and 65 times respectively the amounts which can be dissolved according to Henry's Law. For venous blood the corresponding figures are for carbon dioxide 54 and 20 times, and for oxygen 12 and 41 times. The volume of nitrogen from arterial or venous blood is about 1 per cent., which corresponds to the amount that would dissolve in the blood.

Approximate volumes of gases obtained from arterial and venous blood :

| Gas.                     | Arterial Blood. | Venous Blood. | Difference. |
|--------------------------|-----------------|---------------|-------------|
| Oxygen . . . . .         | 18·8            | 12            | - 6·8       |
| Carbon dioxide . . . . . | 48              | 54            | + 6·0       |
| Nitrogen . . . . .       | 1               | 1             | 0·0         |

If the amount dissolved is not proportional to the partial pressure, then one must attempt to explain the discrepancy by molecular aggregation or by removal of the gas by combination with some other substance.

The amount of carbon dioxide dissolved in salt solution corresponds to solution of the carbon dioxide as a purely physical process, but the amount of carbon dioxide in blood is greatly in excess of the amount that can dissolve in the water of the blood. This, as mentioned in the preceding chapter, is partly due to the union of the carbonic acid, formed on solution of the carbon dioxide, with the alkali of the blood to form bicarbonate.

Similarly, the amount of oxygen in blood is greatly in excess of the amount of oxygen that can dissolve in the same quantity of salt solution. By separating the corpuscles from the plasma it can be shown that the extra oxygen is associated with the red blood corpuscles and more particularly with the haemoglobin in the corpuscles.

We can deal with this problem in two stages : first, the chemical reactions of haemoglobin ; and, secondly, the conditions under which haemoglobin unites with gases.

### Chemistry of Hæmoglobin

After liberation from the red blood corpuscles, hæmoglobin may be caused to crystallize. The hæmoglobin from the blood of some animals is more easily crystallized than that from others. In order to induce crystals to form the solubility must be decreased by various means, such as addition of salts, alcohol, or similar substance, and cooling the mixture to the freezing-point. The easiest crystals to obtain are those of the guinea-pig or rat. Crystals from the blood of these animals may be obtained by placing a drop on a glass microscope slide, adding a drop of distilled water, then ringing the drop with Canada balsam and putting on a cover-glass.

The crystals from different species have different forms (see Fig. 121). The hæmoglobin so obtained is protein containing iron. By hydrolysis it can be split up into an iron-containing portion called hæmatin and a histone-like protein called globin. The former composes about 4 per cent. of the hæmoglobin, and the latter 96 per cent. This hydrolysis is accomplished easily by weak acids or weak alkalies. The iron can be split off from hæmatin by more drastic treatment when a pyrrol-containing substance is left, known as hæmatoporphyrin, which is related to the bile pigments. There are therefore three stages of complexity, namely, that of a coloured protein, hæmoglobin; that of an iron-containing pigment free from protein, hæmatin; and an iron-free pigment, hæmatoporphyrin. These stages are complicated by the fact that hæmoglobin can form compounds with other substances, such as oxygen, carbon monoxide and nitric oxide. As hæmoglobin, its compounds and derivatives show absorption bands in the visible spectrum, these bands are used to characterize the different substances. Although we do not know the relation of chemical constitution to absorption bands in the spectrum, the absorption bands and the changes produced in them by reagents enable us to distinguish certain molecular rearrangements to which various names have been given. These rather complicated relations must be described because of the importance in recognizing changes in the blood as the result of poisons, e.g. carbon monoxide, and the identification of blood derivatives, for example in the urine.

A general test for hæmoglobin is the reaction whereby guaiacum resin or benzidine is oxidized in its presence by hydrogen peroxide.

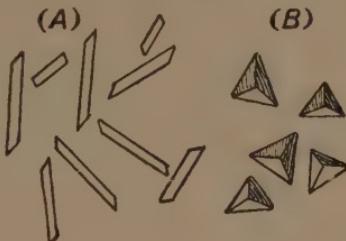


FIG. 121.—(A) Crystals of Oxy-hæmoglobin, Horse, Man or Rat ( $\times 50$ ). (B) Crystals of Oxyhæmoglobin, Guinea-pig ( $\times 50$ ).

In both cases a blue colour is produced. The benzidine test is more delicate and more reliable, as the guaiacum test may be mistaken for the green colour given by the reagents in the presence of iodides.

Another test for haemoglobin is to hydrolyse the haemoglobin to haematin, which can be dissolved by some hot organic solvent, and on cooling crystals of haematin chloride or haemin separate as minute dark brown or black plates (*Teichmann's test*).

The test is performed by placing a drop of blood on a slide with several drops of glacial acetic acid and covering the whole with a cover-glass. The mixture is heated until it boils, then it is allowed to cool. The glacial acetic acid hydrolyses the haemoglobin and the haematin dissolves in the hot glacial acetic acid : the haematin chloride separates when the solvent cools. If chlorides are absent, as when testing an old blood-stain which has been washed, a trace of sodium chloride must be added in order to furnish the chlorine to form the haematin chloride.

In mapping out the absorption spectra of haemoglobin the sodium or D Fraunhofer line is an important landmark : it corresponds to the yellow or brightest portion of the spectrum.

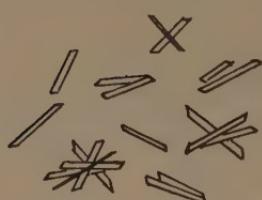


FIG. 122. — Crystals of Hæmin (Hæmatin Chloride) ( $\times 400$ ).

The C, E and F Fraunhofer lines in the red, green and blue respectively are useful in describing the position of the absorption bands of haemoglobin derivatives. The various pigments show their characteristic bands to best advantage in appropriate dilutions. Thus it is necessary to examine the various pigments at different dilutions and not all at the same concentrations.

In what follows it is assumed that the spectra are examined at the most suitable dilutions.

Starting with haemoglobin, we find that it has a purplish colour, and it shows a broad diffuse absorption band between the D and E, lines.

*Oxyhaemoglobin.* On allowing haemoglobin to take up oxygen we obtain the pigment characteristic of arterial blood. This is bright red in colour, but in dilute solution it has a distinctly yellow colour. This oxyhaemoglobin shows a spectrum with two well-defined bands of about equal intensity : the one near the D line is the narrower. The second somewhat broader line extends nearly as far as the E line.

The effect of concentration of solution on the absorption bands can be illustrated by the case of oxyhaemoglobin. With increasing concentration the two bands become wider until they fuse and at the same time the ends of the spectrum are cut off more and more.

If the appearances seen in different dilutions are plotted one can make a curve showing the effect of increase in concentration on the absorption bands. If one contrasts with this the corresponding curve of haemoglobin one sees how in dilute solutions of oxyhaemoglobin the absorption between the D and E lines breaks into the bands, whereas with haemoglobin it remains as one band to the extreme dilution at which any absorption is visible.

Oxyhaemoglobin can be turned into haemoglobin by milk alkaline reducing agents, or by removal of oxygen by a vacuum pump.

*Carboxyhaemoglobin.* Addition of carbon monoxide to haemoglobin gives a spectrum which is almost the same as that of oxyhaemoglobin, but the band near the D line is slightly farther from the

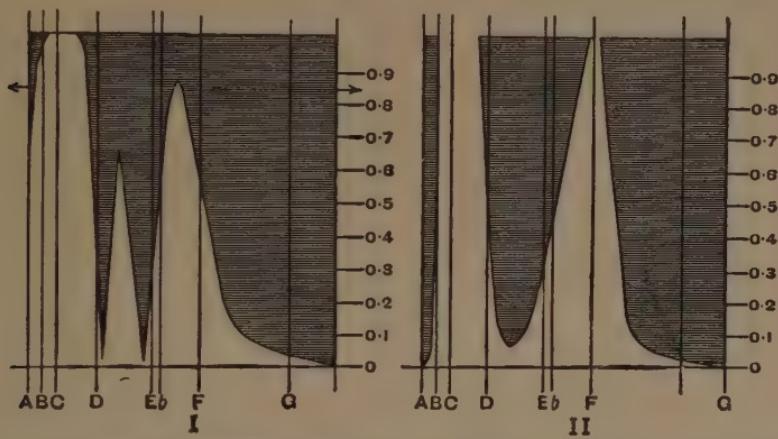


FIG. 123.—Graphic Representation of the Amount of Absorption of Light by Solutions of (I) Oxyhaemoglobin and (II) Reduced Haemoglobin (Rollett from Halliburton's *Handbook of Physiology*, John Murray).

The shading indicates the amount of absorption. The figures on the right express percentages. The letters below indicate the positions of the Fraunhofer Lines. Sections across the diagrams show the appearance of the spectrum at corresponding dilutions. Note the bifurcation of the band in oxyhaemoglobin solutions at about 0.65 per cent., whilst in haemoglobin solutions the band remains single up to the highest dilution in which it is visible.

D line. This slight difference cannot be detected without special methods of examination. The affinity of haemoglobin for carbon monoxide is between two and three hundred times that of its affinity for oxygen; hence carbon monoxide haemoglobin is formed by passing gas containing carbon monoxide through oxyhaemoglobin solution. The carbon monoxide combined with haemoglobin is not readily removed by reducing agents or by a vacuum, hence one can differentiate between carbon monoxide haemoglobin and oxyhaemoglobin by adding a reducing agent; the former shows the two bands practically unchanged, whilst the latter is soon reduced so that the two bands disappear and are replaced by the single band of haemoglobin. A further difference between carbon monoxide haemoglobin and oxyhaemoglobin is that on dilution the former remains a

bright cherry red, whilst, as pointed out above, the latter becomes a distinct yellow colour.

*Nitric Oxide Hæmoglobin.* Hæmoglobin likewise unites with nitric oxide to form nitric oxide hæmoglobin, which has a spectrum like oxyhæmoglobin, only the band near the D line is nearer the D line than that in oxyhæmoglobin (Hartridge). The affinity of hæmoglobin for nitric oxide is even greater than its affinity for carbon monoxide. Nitric oxide hæmoglobin has not the same practical importance as carbon monoxide hæmoglobin. Owing to the frequent presence of carbon monoxide in illuminating and other gases carbon monoxide poisoning frequently occurs.

*Methæmoglobin.* On rendering an oxyhæmoglobin solution faintly acid it becomes brown, and the spectrum alters so that the chief absorption band is now seen in the red of the spectrum near the C line. Methæmoglobin may be formed in other ways, such as by the action of potassium ferricyanide on oxyhæmoglobin. In some specimens faint absorption bands may be visible in addition to the strong band in the red of the spectrum, but they are possibly due to some alkaline methæmoglobin being present.

When methæmoglobin is formed from oxyhæmoglobin by the action of acid, oxygen is given off. This amount of oxygen is half that contained in easily dissociable form in oxyhæmoglobin (Roaf and Smart). When methæmoglobin is reduced by hydrazine hydrate half the amount of nitrogen is obtained that would be given off when oxyhæmoglobin is reduced by hydrazine hydrate (Buckmaster). These two observations suggest that methæmoglobin has lost half the dissociable oxygen contained in oxyhæmoglobin. On rendering methæmoglobin alkaline the colour changes to red, and the spectrum shows three bands. Two of these correspond to the two of oxyhæmoglobin, only they are fainter; the third is linked up with the one near the D line by a shading and it lies just on the red side of the D line.

Methæmoglobin can be easily reduced by reducing agents to hæmoglobin (Haldane).

*Hæmatin.* If hæmoglobin is treated with alkali the globin is split off, leaving hæmatin. Hæmatin shows two absorption bands: a dark narrow band between the D and E lines, but somewhat nearer the E line, and a broader less opaque band which overlaps the E line. This solution has a dark red colour, and the band between D and E is the strongest of any of the hæmoglobin derivatives, i.e. it can be seen at dilutions when the bands of the other compounds would have disappeared.

*Alkaline Oxyhæmatin.* On treating hæmatin with oxygen the colour changes to a yellowish green and the absorption band becomes so faint that it is barely visible in solutions so strong that

most of the spectrum is blotted out. This is called alkaline oxyhaematin: it can be formed by the direct action of alkali on oxyhaemoglobin. In solution in alcohol the band is somewhat more distinct.

*Acid Oxyhaematin.* On treating oxyhaemoglobin with acid stronger than that necessary to form methaemoglobin, the solution turns brown and a band is seen in the red further from the D line than that of methaemoglobin. This is known as acid oxyhaematin. Acid oxyhaematin and alkaline oxyhaematin are interconvertible by changing the hydrogen ion concentration.

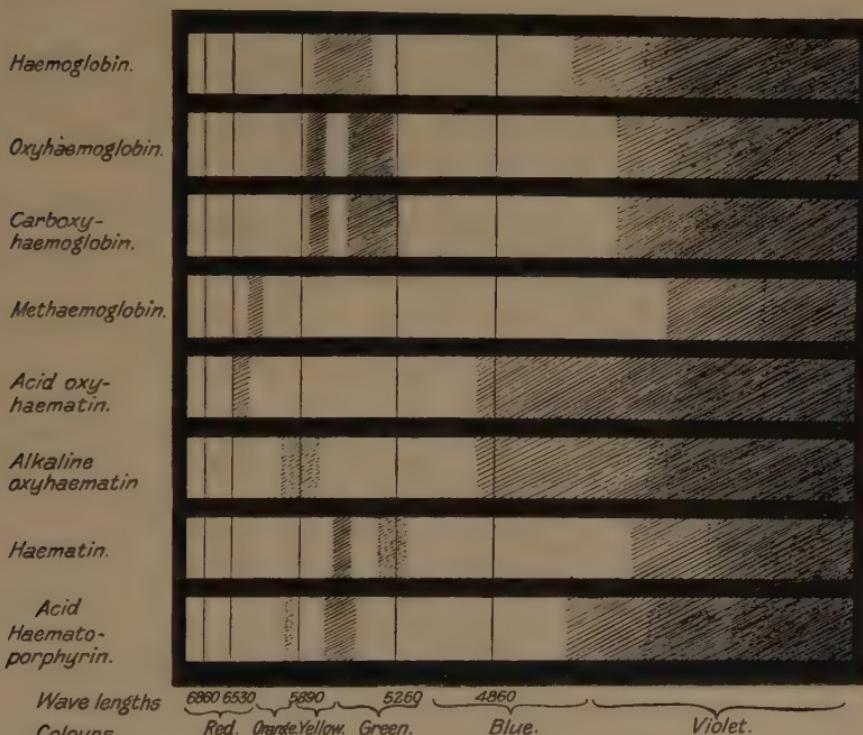


FIG. 124.—Absorption Bands in the Visible Spectrum due to certain Compounds and Derivatives of Hæmoglobin.

*Hæmatoporphyrin.* If some oxyhaemoglobin is dropped into concentrated sulphuric acid a purple colour is seen. This is due to acid hæmatoporphyrin or iron-free hæmatin. The absorption spectrum shows two bands: a broad one between the D and E lines, nearer to the D line, and a narrower one between the C and D lines, but near to the D line. This is probably a derivative of reduced hæmoglobin, as hæmatoporphyrin can be formed by weaker acid from hæmoglobin than from oxyhaemoglobin.

By precipitating the hæmatoporphyrin and dissolving it in alkali

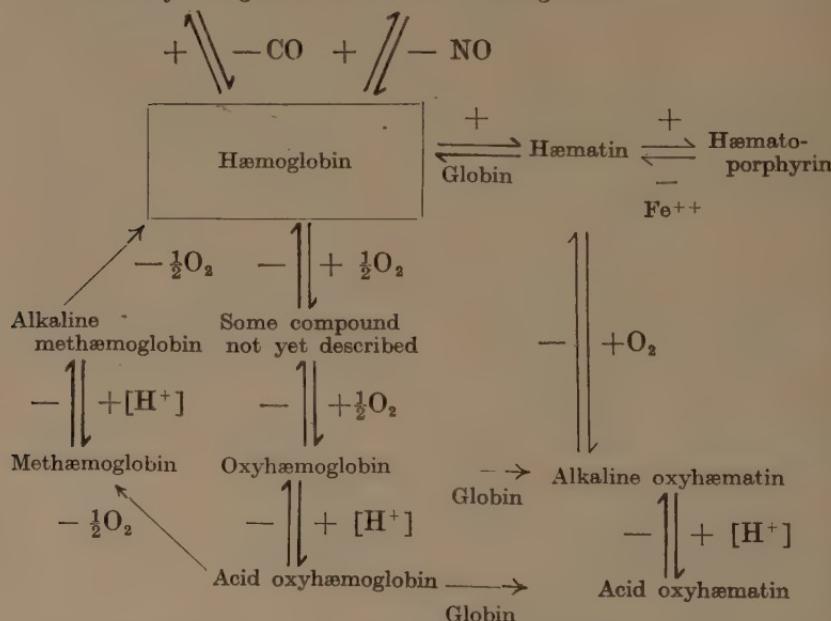
one obtains alkaline haemato porphyrin. This shows four bands : two in the region occupied by the bands of oxyhaemoglobin, one midway between the C and D lines, and another between the E and F lines.

The positions of the bands described above are for solutions in water except in the case of acid haemato porphyrin, which was made in concentrated sulphuric acid. The bands may show slight differences in position from various physical causes, such as the nature of the solvent, temperature, pressure, etc.

The relations described above are shown by the following schema, in which reversible reactions are marked by double arrows. Thus it is possible to form haematin from haemato porphyrin and ferrous salts and haemoglobin from haematin and globin or other proteins (Laidlaw). The peculiar copper-containing pigment found in wing feathers (Turacin) can be formed from haemato porphyrin and copper salts (Laidlaw).

CHART SHOWING RELATIONSHIPS BETWEEN HÆMOGLOBIN, ITS COMPOUNDS AND DERIVATIVES

Carboxyhaemoglobin. Nitric-oxide Hæmoglobin



The identification of a compound can be carried out from the colour of the solution, the absorption bands and its behaviour to reagents mainly by change in hydrogen ion concentration and by reducing agents.

The amount of iron contained in haemoglobin is about 0.4 per cent., which gives for the minimal molecular weight of haemoglobin containing one atom of iron a value of about 14,000.

### THE CONDITIONS UNDER WHICH HÆMOGLOBIN COMBINES WITH OXYGEN

As described in the preceding section, haemoglobin can combine with oxygen to form oxyhaemoglobin and with carbon monoxide to form carbon monoxide haemoglobin. The latter is of importance mainly because it interferes with the carriage of oxygen by haemoglobin, but otherwise it behaves like oxyhaemoglobin, only the compound is more stable.

The amount of oxygen that combines with each gm. of haemoglobin when the latter is fully saturated with oxygen is 1.34 c.c., at 760 mm. Hg. and 0° C. That is equivalent to two atoms of oxygen for each atom of iron in the molecule. As blood contains 14 per cent. of haemoglobin, the volume of oxygen that can be carried by the blood is 18.8 per cent.

If the pressure of oxygen is diminished oxygen is given off, and in a vacuum the whole of the extra oxygen can be recovered from the haemoglobin. The pressure which would be required to keep 18.8 c.c. of oxygen in solution in water is shown in Table XXXVII to be about 8½ atmospheres. Compare this pressure with the pressures shown in Fig. 125, when the haemoglobin is practically saturated with oxygen.

The relation of oxyhaemoglobin formation to the partial pressure of oxygen is usually expressed in the form of a curve. If one represents the partial pressures of oxygen as abscissæ and the amount of oxygen combined with haemoglobin as ordinates, the curve shown in Fig. 125 results.

In the case of solution of oxygen in water the curve would be a straight line of gentle slope. The great increase in quantity of oxygen absorbed due to the presence of haemoglobin is shown by the pressures that would be required to hold as much oxygen in solution in water.

The quantities of oxygen are measured by the methods to be described presently, but in the charts the ordinates are expressed as percentages. This merely means that the total volume of oxygen absorbed by haemoglobin at a high (atmospheric) pressure of oxygen is taken as 100 per cent. The quantity of oxygen actually obtained at any specified pressure is expressed as a percentage of the quantity obtainable when the haemoglobin is fully saturated with oxygen. The length of the ordinates below the curve show the percentages that the observed amounts of oxygen form of the maximum possible oxygen, whilst the ordinates above the curve show the additional

amounts of oxygen, which can be taken up at higher pressures expressed as a percentage of the maximum possible oxygen for the amount of haemoglobin in the solution. The form of the curve depends upon such factors as the temperature at which the experiment is carried out, and the amount and nature of electrolytes

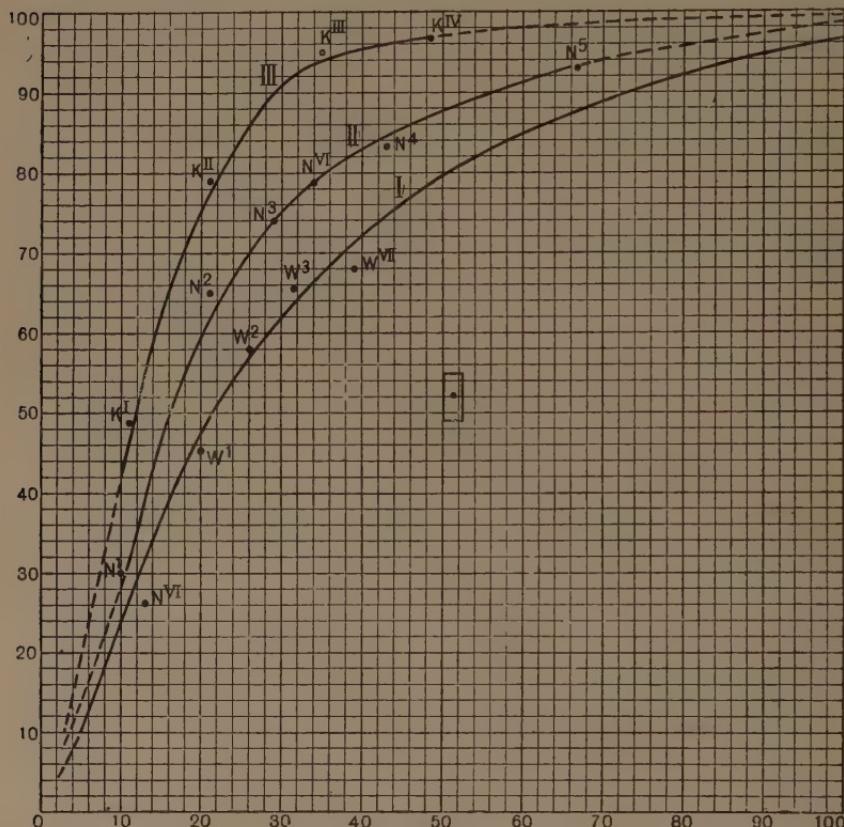


FIG. 125.—Effect of Salts on the Dissociation of Oxyhaemoglobin (Barcroft, *Journal of Physiology*).

I. Dissociation curve of oxyhaemoglobin dissolved in water.

II. Dissociation curve of oxyhaemoglobin dissolved in 0.7 per cent. NaCl.

III. Dissociation curve of oxyhaemoglobin dissolved in 0.9 per cent. KCl.

Ordinates = percentage saturation of haemoglobin with oxygen, abscissæ = tension of oxygen in millimetres of mercury. Rectangle surrounding point = magnitude of experimental error. Temperature 37°–38° C.

present. Barcroft has shown that the different shapes of curves obtained from the bloods of different species of animals can be imitated by the same solution of haemoglobin if it has dissolved in it the electrolytes characteristic of the corpuscles of the various species.

The commencement of the curve is convex towards the axis of

the abscissæ. As pointed out by Bohr, this implies that the equilibrium is proportional to some power above unity of the oxygen pressure. This can be explained as the combination of one molecule of oxygen with hæmoglobin followed by a combination of the substance so formed with a second molecule of oxygen. As pointed out above, one molecule of oxygen combines with the amount of hæmoglobin containing one atom of iron. We are driven to the conclusion that the molecule of hæmoglobin contains two atoms of iron. In the schema on p. 246 we have represented it as containing one atom of iron, hence the symbol of  $\frac{1}{2}\text{O}_2$  in the oxidation and reduction of hæmoglobin. We have evidence in the case of methæmoglobin that compounds exist containing only half the replaceable oxygen of oxyhæmoglobin.

If hæmoglobin consists of molecules containing two atoms of iron the osmotic pressure of hæmoglobin, which under some conditions corresponds to a molecule containing one atom of iron must be due to an ionizing salt similar to congo red. Bayliss found that the osmotic pressure of congo red agreed with its molecular weight as calculated from its formula, but that this osmotic pressure was a balance between ions formed by dissociation and an aggregation of the congo red to form masses of greater molecular weight than that corresponding to the structure of the compound.

One factor has a predominant influence on the oxyhæmoglobin dissociation curve, namely the concentration of hydrogen ions in the solution. This is illustrated by the curve showing the oxyhæmoglobin curves with different pressures of carbon dioxide. It is seen that with increasing pressure of carbon dioxide the oxyhæmoglobin curve becomes flatter and approaches a straight line. This effect of carbon dioxide is important in connection with gas exchange in the tissues and lungs.

The pressure of carbon dioxide in the blood increases as it passes through the capillaries of the tissues, which increase is equivalent to changing the oxyhæmoglobin dissociation from one curve to another. For instance, if in Fig. 126 the pressure of carbon dioxide changed from 20 to 40 mm. Hg and the oxygen saturation had been 80 per cent. at the lower pressure, then in order to keep the same amount of oxygen combined with hæmoglobin the oxygen pressure must be increased from about 35 to 45 mm. Hg. This increase in oxygen pressure causes oxygen to be given off more readily to the tissues. The converse occurs in the lungs where carbon dioxide pressure decreases, with the result that for the same oxygen pressure a larger amount of oxygen will be combined with hæmoglobin. This change can be seen in Fig. 126 by tracing a vertical line from one curve to another. For example, at 40 mm. Hg pressure of oxygen a decrease of carbon dioxide pressure from

40 to 20 mm. Hg would cause an increase in oxygen saturation from about 75 per cent. to 85 per cent. This effect of carbon dioxide aids the absorption of oxygen in the lungs and its discharge to the tissues.

**Mathematical Formulae for the Dissociation of Oxyhaemoglobin.** It is possible to obtain a mathematical formula to fit any regular curve but the interest of such a formula is that it may help one to understand the chemical processes underlying the change

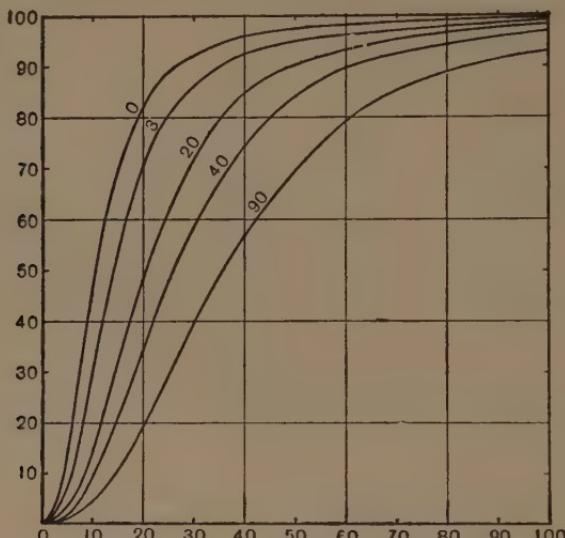


FIG. 126.—Oxyhaemoglobin Dissociation Curves of Human Blood exposed to 0, 3, 20, 40 and 90 Millimetres of Carbon Dioxide (Barcroft, *Journal of Physiology*).

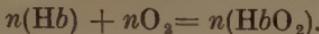
|                                      | Ordinates = percentage saturations of haemoglobin, abscissæ = oxygen pressures. |                      |                      |                      |                 |
|--------------------------------------|---|----------------------|----------------------|----------------------|-----------------|
| Pressures of $\text{CO}_2$           | 0   | 3                    | 20                   | 40                   | 90              |
| Vol. of $\text{CO}_2$ dissolved c.c. | 0.00  | 0.20                 | 1.34                 | 2.69                 | 6.05            |
| Carbonic acid $N \times 10^{-4}$     | 0.0   | 0.9                  | 6.0                  | 12.0                 | 27.0            |
| Hydrogen ion concentration N         | $1 \times 10^{-8}$  | $0.4 \times 10^{-8}$ | $2.4 \times 10^{-8}$ | $4.8 \times 10^{-8}$ | $1.1 = 10^{-7}$ |

represented by the curve. The formula should be a shorthand representation of the changes taking place in the solution. That formula which gives the best analysis of the phenomena is the one to be preferred. The following has been suggested as the formula for the dissociation of oxyhaemoglobin,

$$\frac{y}{100} = \frac{\text{K}_\text{H}x^n}{1 + \text{K}_\text{H}x^n} \quad (\text{A. V. Hill})$$

where  $x$  = pressure of oxygen,  $y$  = proportion of haemoglobin which exists in the form of oxyhaemoglobin and  $n$  = degree of aggregation of haemoglobin.

The chemical equation on which this is based is



$K_H$  is used to designate the constant for Hill's equation, but, unlike most constants in physico-chemical processes, it varies with the conditions of the experiment, i.e. it contains some variables, which amongst other things depend on the acidity of the solution.

Owing to the fact that haemoglobin and oxyhaemoglobin behave as if they were acids, the total amount of haemoglobin cannot be represented merely as  $\text{Hb} = \text{HbO}_2 = 100$ , and as the mass law is concerned with active masses one must consider the dissociations  $[\text{H}^+] [\text{Hb}^-] = K_1[\text{HHb}]$  and  $[\text{H}^+] [\text{HbO}_2^-] = K_2[\text{HHbO}_2]$ . Therefore the total amount of haemoglobin will contain at least the terms

$$[\text{Hb}^-] + [\text{HHb}] + [\text{HbO}_2^-] + [\text{HHbO}_2] = 100$$

or  $[\text{Hb}^-] (1 + [\text{H}^+]/K_1) + [\text{HbO}_2^-] (1 + [\text{H}^+]/K_2) = 100$  and the term  $y$  plotted on the dissociation curves probably represents  $[\text{HbO}_2^-] (1 + [\text{H}^+]/K_2)$ .

**Measurement of Partial Pressure of Gases.** The partial pressures of gases in a solution are measured by analysis of the gases in the space above the solution when the two are in equilibrium. One method of doing this with blood is to fill a cylindrical separating funnel with gas of about the composition that corresponds to the gases in blood. Place a small quantity of blood in the cylinder, lay it on its side and rotate it so that the blood is spread out in a thin layer over the walls of the tube. Analysis of the gas and of the blood will show the partial pressures corresponding to the quantities of gas contained in the blood.

The pressures of gases in circulating blood can be determined by Krogh's microtonometer (see Fig. 127). A narrow tube opens into a wider tube by a conical junction. A small bubble of gas, 2, Fig. 127, is placed in the conical junction. A jet of blood is directed against the bubble of gas so that it is kept moving in the blood and the blood flows away by an opening in the larger tube 1, Fig. 127. Owing to the small size of the bubble it soon reaches equilibrium with the pressures of gas in blood. The bubble is drawn into the narrow tube, 3, by a screw piston, 4, attached to its upper end. The gas is analyzed by measuring the length of the bubble by means of a scale on the narrow glass tube. The gases are absorbed in the usual way and the percentage composition calculated from the volumes absorbed.

Owing to the small size of the bubble the pressure in it is greater than the pressure surrounding it (see p. 155); hence the gases would be absorbed by the blood and the bubble would disappear. The pressure in the apparatus must be decreased by the constant

pressure suction apparatus shown by the three vessels on the right of Fig. 127. A suction is maintained through tube, 15, and the pressure is regulated by the mercury trap, 13; when the pressure becomes too low air is sucked in through tube 14. A pressure gauge, 12, shows the pressure below that of the atmosphere.

**Methods for the estimation of Blood Gases.** When oxyhaemoglobin is exposed to a low pressure of oxygen it dissociates liberating oxygen. This is of fundamental importance in connection with the function of oxyhaemoglobin in the body. The dis-

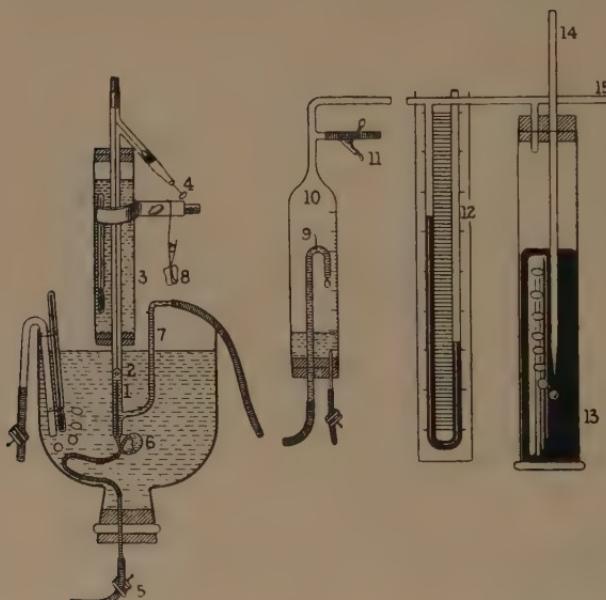


FIG. 127.—Schematic Representation of Krogh's Microtonometer (Flack and Hill). (For description see text.)

sociable amount of gas is the limit for the transport of that gas in the blood.

A mercury pump is therefore the standard instrument for studying the gases of blood. By pumping the gases out of blood they may be measured and analyzed. The principle of the mercury pump is a subject to be studied in physics and the methods of gas analysis have been described on p. 216. The technique is difficult, but the method is the foundation on which our knowledge of the subject is based.

Simpler methods have been developed and their accuracy has been well tested against the results obtained by the mercury pump. The basis of the modern method is the discovery by Haldane that when methaemoglobin is formed by the action of ferricyanide on

oxyhaemoglobin the amount of oxygen liberated is the same as that which would have been obtained by the mercury pump from the same haemoglobin.

*Dupré's Ureometer.* The method shown in Fig. 128 is the same in principle as that of the Dupré ureometer. Ferricyanide does not act upon oxyhaemoglobin contained in the corpuscles, hence the blood must be haemolyzed. Thirty cubic centimetres of a very dilute ammonia solution is placed in the bottle. Twenty cubic centimetres of blood are run in below the ammonia. Four cubic centimetres of a saturated solution of potassium ferricyanide are placed in the small tube B. The liquids in the measuring and levelling tubes are brought to the same level and the burette read. The tap of the apparatus is now turned so that the gas burette is in communication with bottle A and both are closed from the surrounding atmosphere. The ammonia and blood are mixed in order to haemolyse the corpuscles. After haemolysis is complete the ferricyanide tube B is upset and the bottle shaken. After a short interval of time the tubes are levelled and the increase in volume in the gas burette is measured. This volume multiplied by five gives the volume of oxygen obtainable from 100 c.c. of blood.

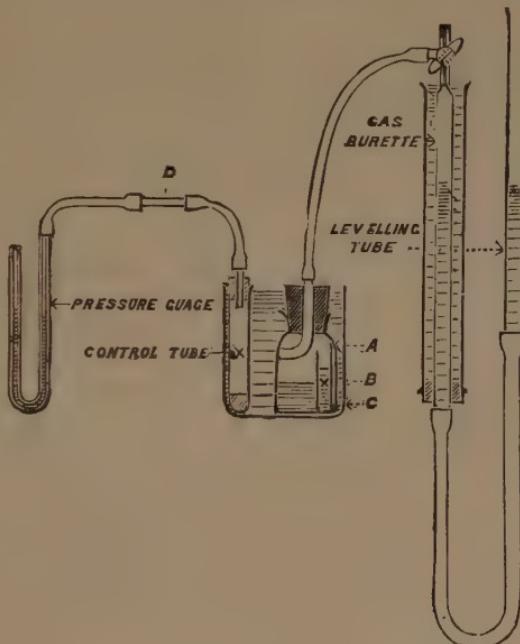


FIG. 128.—Ferricyanide Method of Estimating the Oxygen Capacity of Blood (Pembrey). (For description see text.)

The conditions may be altered according to the object of the experiment. If one wishes to measure the *oxygen capacity* of a sample of blood the sample must be shaken with air and the sample may be haemolysed before the apparatus is closed. If the *oxygen content* of a sample of blood, for instance from an artery, is required, the blood must be collected and transferred to the apparatus without allowing it to come into contact with air. The blood should be run under the surface of the ammonia solution and not mixed

until the apparatus has been closed and the volume in the burette has been noted.

The same apparatus can be used for the estimation of carbon dioxide. After the oxygen has been determined the small tube is lifted out empty and replaced containing 4 c.c. of a saturated solution of tartaric acid. In this case the increase in volume is due to the carbon dioxide liberated by the acid. After correction for the volume of carbon dioxide remaining in the solution the result shows the volume of carbon dioxide in the sample of blood used.



FIG. 129.—Barcroft's Differential Blood Gas Apparatus.

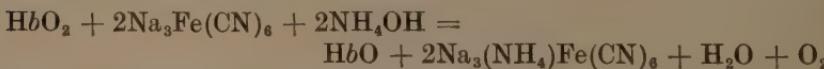
The ammonia and blood are placed in the pear-shaped vessels and the ferricyanide in the small cup shown in the upper part of the pear-shaped vessels.

*Barcroft's Apparatus.* Barcroft has altered the apparatus so that by measuring a small difference in pressure of clove oil and using a small vessel the analysis may be carried out, using only one-tenth of a cubic centimetre of blood.

Fig. 129 shows Barcroft's *differential* blood gas apparatus. It consists of a double apparatus by which simultaneous analyses may be performed on arterial and venous blood. The manometer is shared by the two, hence the difference in pressure is due to the difference in the two samples of blood, e.g. the amount of oxygen lost by blood flowing through an organ.

*Van Slyke's Method.* In this method reduced pressure is used to draw off the gases, hence it does not need any correction for the amount of gas remaining dissolved in the liquids.

The chemical equation for the reaction with ferricyanide may be written:—



$\text{HbO}_2$  representing oxyhaemoglobin and  $\text{HbO}$  methaemoglobin.

**Estimation of Hæmoglobin.** Hæmoglobin is estimated colorimetrically. Twenty cu. mm. of blood are drawn up in the capillary pipette, B in Fig. 130. This is run into some distilled water in the graduated tube, C, whereby the blood is hæmolyzed.

The standard solution is ox blood saturated with carbon monoxide, D. Therefore the hæmolyzed blood must be saturated with carbon monoxide by passing illuminating gas through it. The two carboxy-hæmoglobin solutions are now compared colorimetrically. The

sample in the graduated tube is diluted until it matches the standard.

The physiological value of haemoglobin is its ability to combine with oxygen. The standard is made of such a strength that when the diluted sample matches it at the mark 100 the specimen of blood under examination will have an oxygen capacity of 18.5 c.c. per 100 c.c.

The tube C is graduated in terms of this standard; they are therefore percentages of 18.5 c.c. per 100 c.c. A reading of 90 would have an oxygen capacity of  $\frac{90}{100}$  of 18.5 = 16.7 c.c.



FIG. 130.—Gowers-Haldane Hæmoglobinometer.

A = bottle of distilled water, B = capillary pipette, C = comparison tube, D = standard solution of carboxyhaemoglobin, F = lancet for pricking skin.

### Tests for Blood

It is sometimes important to be able to recognize the presence of blood. The tests for blood depend on the presence of cells, the presence of haemoglobin and certain biological characters.

*Microscopical Test.* Whole blood can be recognized by the distinctive shapes of the blood corpuscles. This test does not apply when the corpuscles are destroyed.

*Spectroscopic Test.* If an appreciable quantity of blood pigment is present the colour will suggest some derivative of haemoglobin. The solution should be examined by the spectroscope. In doubtful cases heat with alkali, then reduce the solution. The spectrum of haematin can be recognized in a higher dilution than any other haemoglobin derivative.

*Hæmin-Crystals.* This test has been described on p. 242.

*Colour Tests for Blood.* A drop of tincture of guaiacum or guaiacolic acid is added to dilute solution of haemoglobin. When the mixture is treated with hydrogen peroxide a blue colour results even if the haemoglobin solution had been previously boiled. Oxidases may produce a similar colour but they are destroyed by boiling, hence the importance of the colour reaction after the solution has been boiled. Instead of guaiacum, benzidine or phenolphthalein may be used. The former (*Adler's test*) gives a blue, the latter a red colour.

*Biological Test.* This is used to distinguish between the blood of different species (see p. 549).

#### TRANSPORT OF CARBON DIOXIDE IN THE BLOOD

Carbon dioxide is contained in the blood in the form of dissolved carbonic acid and as sodium bicarbonate. The former must be present as the blood has a partial pressure of carbon dioxide so there must be a certain amount of carbonic acid in physical solution. The amount of carbon dioxide in solution is however much greater than that which can dissolve in water or salt solution, so it must be held in some other form.

If defibrinated blood is exhausted by a vacuum pump all the carbon dioxide can be obtained from it, but if the serum is separated from the corpuscles and the serum exhausted by the same pump only a small amount of carbon dioxide will be given off. The whole of the carbon dioxide can be obtained if acid is added to the serum : thus the corpuscles act as if they contained an acid.

The explanation offered is that serum contains bicarbonate. When one attempts to remove carbon dioxide from bicarbonate, carbonate is formed, so that the pressure of carbon dioxide becomes very low and the solution becomes more alkaline.

When carbon dioxide is added to blood the corpuscles increase in size and an exchange of chloride ions takes place between the corpuscles and serum. Thus the amount of bicarbonate is increased because the sodium ions are left behind to combine with the carbon dioxide. Although venous blood contains more total carbonic acid than arterial blood comparatively little difference is found between the serum of arterial and venous blood, therefore most of the extra carbon dioxide is carried in the corpuscles.

The addition of oxygen to blood raises the tension of carbon dioxide (Christiansen, Douglas and Haldane). This increase in tension aids the escape of carbon dioxide from the blood into the lung alveoli in the reciprocal manner to which carbon dioxide aids the exchange of oxygen (see p. 249). There are two ways in which

this change of carbon dioxide pressure on the addition of oxygen can be explained. One is that oxygen and carbon dioxide are both competing for haemoglobin so that the addition of one tends to displace the other. The other explanation is that haemoglobin is an acid substance competing with carbonic acid for the bases of the corpuscle. Oxyhaemoglobin is a stronger acid than reduced haemoglobin, therefore addition of oxygen will allow the oxyhaemoglobin to obtain a larger quantity of the base, thus setting free carbonic acid with a consequent rise of carbon dioxide tension. When the concentration of carbon dioxide is increased it obtains a larger quantity of base, the oxyhaemoglobin loses the base, and it may be more unstable when uncombined with base, hence the pressure of oxygen is increased (see p. 249).

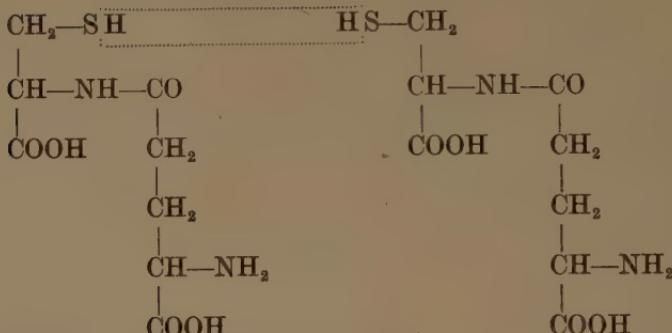
Apart from these speculations we must recognize that some substance in the corpuscle must be able to absorb base as the whole of the carbon dioxide can be obtained from blood in a vacuum. Whether this is due to the haemoglobin or to some other constituent of the corpuscle is not universally agreed upon.

The more probable explanation is that the haemoglobin acts as an acid and that oxyhaemoglobin acts as a stronger acid than haemoglobin.

#### INTERNAL RESPIRATION OR OXIDATION IN THE TISSUES

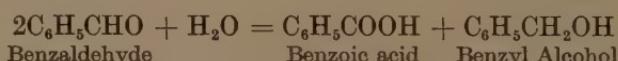
We have seen how the gases are transported in the blood and the conditions under which the gases are given off. The circulation through the capillaries is slow, about 0·5 mm. per second, so that the exchange takes place under as favourable conditions as possible. The tissues are always using up oxygen and giving off carbon dioxide, therefore we see that the diffusion of gases will occur. Diffusion takes place between the lymph and tissues, then between the lymph and plasma and finally between the plasma and corpuscles.

Under resting conditions the tissues absorb oxygen and excrete carbon dioxide. The materials oxidized in the tissues are not acted on by molecular oxygen outside the body, therefore we must look for some means whereby the oxygen can be made more active. The processes of oxidation in the tissues have been assumed to be due to oxidizing enzymes, but the isolation from many types of tissue of a compound of cysteine and glutamic acid, glutathion, suggests an alternative explanation. Hopkins isolated this cystein-glutamic acid and found that it could exist in two forms, one of which was a single molecule of cysteine with a single molecule of glutamic acid, the other consists of two molecules of each. The relation of the two forms is shown by the formulæ:—



Cysteil-glutamic acid and its conversion into cystil-glutamic acid by oxidation (Quasted, Stewart and Tunnicliffe).

In the condition of a dipeptide it can take hydrogen from some hydrogen donor, such as water, if an oxygen acceptor is present to take the oxygen. The dipeptide forms two molecules of the peptide when reduced, but they can be easily oxidized to form the dipeptide. It is probable that oxidation in the tissues may be brought about by oxidation of the peptide to dipeptide by molecular oxygen, then the dipeptide will take hydrogen from water at the same time that the oxygen of the water is used to oxidize some other substance, e.g. glucose. This is analogous to the familiar Cannizarro reaction in which two molecules of benzaldehyde react forming one molecule of benzyl alcohol and one of benzoic acid. One molecule of benzaldehyde acts as a hydrogen acceptor and the other as an oxygen acceptor, the hydrogen and oxygen being furnished by water.



This behaviour does not exclude the action of an enzyme as one view of enzyme action is that some intermediate reaction takes place, but in this case there is a definite chemical substance involved, whilst in enzyme actions no definite chemical substance is known. The reactions of the peptide and dipeptide can be shown by means of the action of extracts of tissues on methylene blue. The methylene blue is reduced to a colourless substance by the di-peptide. The peptide is a sulphhydrate and the reduced form can be shown in solution by the purple colour given with sodium nitroprusside.

When a tissue shows increased activity the amount of oxygen taken is always increased. How this is brought about is not yet known as it may be due to one of several causes, namely :—

1. An increased pressure of oxygen.
2. An increased amount of oxidizable material.
3. An increased rate of removal of the products of oxidation.

4. An increase in the amount of oxidase or in the activity of the glutathione reaction so that the rate of oxidation is increased.

These are all dependent on the equilibrium equation :—

$$\frac{C_A \times C_x}{C_y} = \frac{k'}{k''} = K$$

where  $C_A$  = concentration of active oxygen,  $C_x$  = concentration of oxidizable substance,  $C_y$  = concentration of products of oxidation, e.g.  $\text{CO}_2$ ,  $k'$  and  $k''$  are velocity constants and  $K$  the equilibrium constant. If the reaction is not in equilibrium an increase in the constants  $k'$  and  $k''$  will increase the rate of oxidation, whilst the concentrations of the various reacting substances as stated in 1, 2 and 3 will cause an increase in rate or even upset an equilibrium condition if it already exists.

The conditions which govern increased activity must be left for consideration until we are dealing with regulating mechanisms in the next part of this book.

For further details the student should consult J. Barcroft, *Respiratory Function of the Blood* (Cambridge Press).

## CHAPTER XX

### INTERMEDIATE METABOLISM : LIVER AND SPLEEN

We have traced the food substances until they are absorbed, we have studied the end products of metabolism and we have seen how the energy exchange can be quantitatively measured. In the present chapter we shall attempt to find out what chemical steps occur during the intermediate stages of metabolism.

#### CARBOHYDRATE METABOLISM

Carbohydrate is so easily and completely oxidized in the normal body that it is difficult to find any intermediate substances between glucose and carbon dioxide and water. Lactic acid is found in many active tissues and it seems probable that this is one of the stages in the breakdown of glucose. Pyruvic aldehyde may be formed from glucose by alkali and pyruvic aldehyde can be turned into lactic acid by alkali. Pyruvic aldehyde may therefore be a link between glucose and lactic acid. Glyceric aldehyde may be intermediate between glucose and pyruvic aldehyde. There is on the other hand some evidence that glucose is oxidized before being split into the above three carbon compounds.

One of the difficulties in the investigation of carbohydrate metabolism is that the substances formed seem to be all extremely soluble, hence difficult to isolate.

At one time it was believed that glycuronic acid was the first stage in the oxidation of glucose. When camphor is fed to animals it is excreted in the urine as campho-glycuronic acid. The toxicity of camphor is diminished by concomitant administration of glucose. It seems that the conjugation of camphor with glycuronic acid is a defensive mechanism like the formation of conjugated sulphates (p. 204) and of hippuric acid. Glycuronic acid is not believed to be a stage in the normal oxidation of glucose.

#### METABOLISM OF FATS

There is much more information about the oxidation of fats. This seems to be due to the greater ease of isolation of the intermediate products. The general method is to make some hypothesis as to the possible intermediate stages of metabolism. One

may then attempt to isolate these intermediate substances or administer them and see if the normal end products are produced. Certain cases of congenital abnormalities of metabolism are important as these individuals excrete abnormal substances which may be normal intermediate products.

In the case of fats the first significant point is that all natural fats contain fatty acids with an even number of carbon atoms. This suggests that fatty acids (above the three-carbon stage) are built up and oxidized so that two carbon atoms form a unit. This is expressed in *Knoop's theory of  $\beta$ -oxidation*. The carbon atom next but one to the carboxyl group is oxidized with the splitting off of two carbon atoms at a time. The  $\alpha$ -carbon atom is the one next to the carboxyl group and the  $\beta$ -carbon atom is the second one.

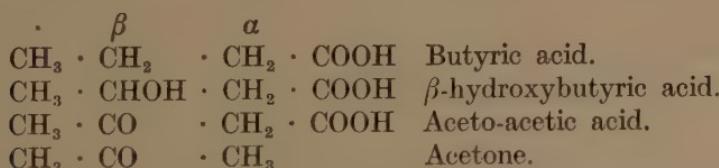
Evidence in support of  $\beta$ -oxidation is found in two types of experiment.

(1) Fatty acids united to an aromatic nucleus are oxidized and excreted in the urine united with glycine. Two substances are found, namely hippuric acid (benzoyl-glycine) and phenyl-aceturic acid (phenyl-acetyl-glycine), depending on whether the fatty acid united to the benzene group contained an odd or an even number of carbon atoms. This is most easily explained by removal of two carbon atoms at a time from the carboxyl end of the fatty acid chain.

(2) Perfusion of various fatty acids through the liver furnishes further evidence. Butyric acid is not so easily oxidized as other fatty acids. When excessive amounts of fat are being oxidized or when metabolism is abnormal due to failure to burn carbohydrate, derivatives of butyric acid appear in the urine. It seems that the oxidation of butyric acid requires the concomitant oxidation of glucose.

Perfusion of various acids through the liver gives rise to derivatives of butyric acid if the original acid contains an even number of carbon atoms. If the original acid contains an odd number of carbon atoms butyric acid is not formed.

The derivatives of butyric acid found in the above experiment or in the urine when the oxidation of fats is abnormal are themselves products of  $\beta$ -oxidation.



Aceto-acetic acid can lose carbon dioxide and give rise to acetone.

Acetone is usually found in the urine with these substances. Hence they are called "acetone" bodies.

*Test for  $\beta$ -hydroxybutyric Acid.* This can be recognized by its dextrorotatory action on polarized light, other substances having been removed.

*Test for Aceto-acetic Acid.* A claret colour is given with ferric chloride similar to the colour given by salicylates, etc.

*Test for Acetone.* Saturate the solution with ammonium sulphate, add a few drops of a dilute solution of sodium nitroprusside and some strong ammonia. A permanganate colour is given (Rothera).

**Ketogenic and Antiketogenic Substances.** The linked oxidation of fats and glucose has been investigated by Schaffer. When glucose is not being oxidized in the animal body "acetone" bodies are formed. By comparing the amount of glucose required for the concomitant oxidation of fats he has found that one molecule of glucose oxidized is accompanied by the oxidation of two molecules of fatty acid in the body. Similarly one molecule of glucose is responsible for the oxidation of two molecules of aceto-acetic acid *in vitro*.

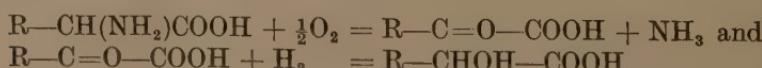
On the other hand one molecule of glyceric aldehyde and similar three-carbon-containing compounds each aids the oxidation of two molecules of aceto-acetic *in vitro*.

If glucose is split into two three-carbon groups it ought to be able to aid the oxidation of four molecules of fatty acid. It is for this reason that Schaffer suggests that glucose is oxidized before splitting into two three-carbon substances. He suggests that lactic acid is only formed under asphyxial or non-oxidative conditions such as muscle contraction and other rapid activities. In the diabetic organism the reaction proceeds in the direction of lactic acid to glucose. The view he puts forward is that in the presence of oxygen, lactic acid and pyruvic aldehyde are turned into glucose.

#### METABOLISM OF PROTEINS

This amounts to the metabolism of amino-acids. There are such a number of amino-acids that a full discussion is hardly possible.

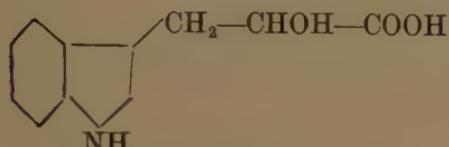
The amino-acids are probably de-aminised by oxidation to form  $\alpha$ -keto-acids. The keto-acids may be asymmetrically reduced to  $\alpha$ -hydroxy-acids :—



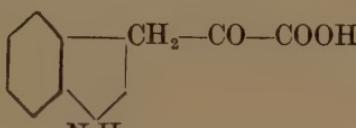
The keto-acids are oxidized completely and the hydroxy-acids may be bye-products of the normal oxidation. By removal of carbon dioxide from amino-acids bases are formed.

Two examples follow to show the intermediate steps in the oxidation of some special amino-acids.

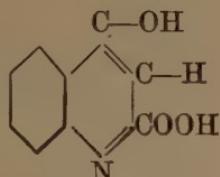
*Kynurenic acid* is a normal constituent in the urine of dogs. It is the result of the metabolism of tryptophane. The intermediate stages might be either indol-lactic acid or the corresponding keto-acid. The former, however, is toxic and is not oxidized to kynurenic acid whilst the latter does give rise to kynurenic acid. This is one step in the chain of evidence which indicates that the keto-acids are the intermediate stage in the oxidation of amino-acids.



Indole-lactic Acid.

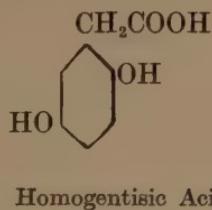
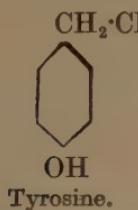


Indole-pyruvic Acid.



Kynurenic Acid.

*Homogentisic Acid.* In certain individuals a congenital condition exists in which their urine turns black on exposure to air. Their health is not greatly interfered with but the condition is discovered in infancy because it is noticed that the linen becomes stained black (alkaptonuria). It has been found that the coloration is due to the spontaneous oxidation of homogentisic acid and that the amount of the latter depends on the amount of tyrosine in the diet.



This is an interesting example because it shows the oxidation of the amino group to form an acid with the loss of one carbon atom and a shifting of the hydroxyl group on the benzene ring.

Normally homogentisic acid is completely oxidized and aromatic substances of similar structure are also oxidized. In alkaptonuria the defect is in the ability of the organism to oxidize homogentisic acid.

## INTERCONVERSION OF CARBOHYDRATES, FATS AND PROTEINS

It can be shown that carbohydrates can be converted into fats. Experiments by Lawes and Gilbert proved that more fat can be recovered from the body of an animal than was present in the food. The extra fat was derived from the carbohydrate.

Glucose can be converted into pyruvic aldehyde by dilute alkali and Smedley and Lubrzynska have shown that pyruvic acid may be the starting-point for the synthesis of fatty acids, adding two carbon atoms at each step.

By the conversion of carbohydrate into fat a more concentrated store of energy is produced. At least  $2\cdot27$  grams of carbohydrate are required to form one gram of fat ( $2\cdot27 \times 4\cdot1 = 9\cdot3$ ). During the process the carbohydrate is reduced. The oxygen removed from the carbohydrate is used to oxidize other carbon compounds with the result that carbon dioxide will appear in the expired air without a corresponding absorption of oxygen.

The respiratory quotient is the resultant of all the oxidative processes in the body. A respiratory quotient greater than unity must be due to the conversion of carbohydrate into fat. A temporary rise in respiratory quotient may be the result of a washing out of preformed carbon dioxide by excessive breathing or by production of acid. During preparation for hibernation an animal may form fat. In such cases the respiratory quotient would be raised.

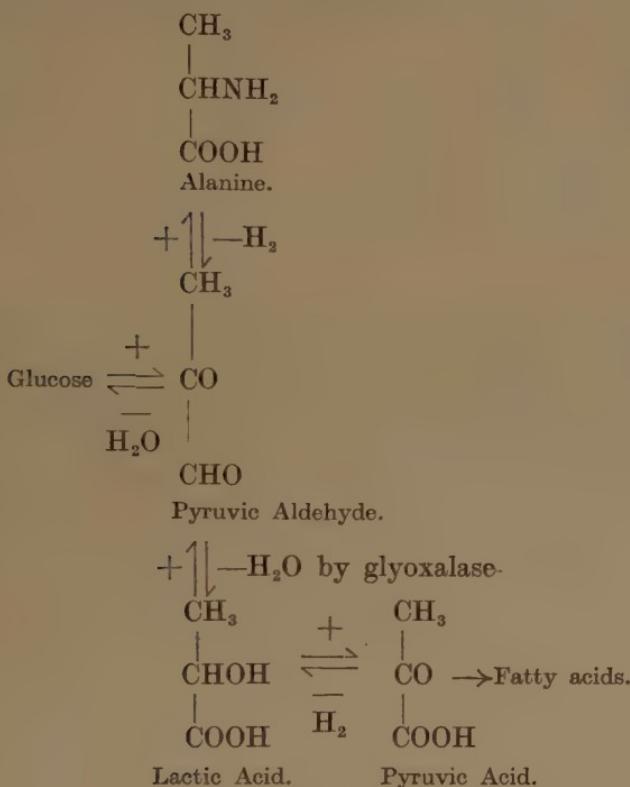
The reverse condition, namely a conversion of fat into carbohydrate, will give a low respiratory quotient. It has never been proved that fat can be converted into carbohydrate. The fact that fat metabolism is deranged if the oxidation of sugar is not taking place at the same time suggests that fat may not be converted into glucose.

Some amino-acids can be converted into sugar. Thus in an animal rendered glycosuric by phlorizin all the carbon of glycine and alanine can be converted into glucose and three-quarters and three-fifths of the carbon of aspartic and glutaminic acids respectively. This shows how amino-acids might be turned into fats through glucose although it is improbable that much fat is formed from amino-acids.

Alanine can be turned into pyruvic aldehyde and thus into lactic acid ; the latter change is accomplished by an enzyme which is called glyoxalase.

Synthesis of amino-acids can be shown by perfusion of an excised liver with the ammonium salts of keto-acids whereby such simple amino-acids as alanine can be formed. The amino-acids containing aromatic groups cannot be synthesized in the body.

The inter-relations between carbohydrates, fats and proteins are summarized in the following schema :—



*Note.*  $-\text{H}_2$  = oxidation.  $+\text{H}_2$  = reduction. In the interchange between alanine and pyruvic aldehyde  $\text{NH}_2$  is taken as equivalent to one hydrogen atom.

### LIVER

Many of the intermediate changes in metabolism occur in the liver and they will be discussed in relation to the function of the liver.

The liver consists essentially of blood spaces into which have grown tubules until the whole has assumed the appearance of a solid glandular structure. The blood supply comes from two sources. (1) The portal vein which brings blood from the intestine and spleen; by this channel the food products absorbed by the blood in the intestinal wall are carried directly to the liver. (2) The hepatic artery which brings arterial blood to the liver, thus supplying oxygen, and any materials which may be present in the systemic circulation.

The blood from these two vessels mixes and after flowing through capillary-like spaces (sinusoids) it is collected into hepatic veins which ultimately drain into the inferior vena cava.

**Structure.** In order to understand the relation of the cells to the blood we must know something about the structure of the liver. The blood-vessels, the bile ducts, lymphatics and nerves enter the liver at the hilus ensheathed in a prolongation of the fibrous capsule of the liver known as Glisson's capsule. The connective tissue divides the liver into lobules, which are best seen in sections of pig's or foetal human liver. Thus the portal and hepatic artery



FIG. 131.—Photomicrograph of Pig's Liver ( $\times 40$ ).

The connective tissue outline of the lobule is shown. In the centre of the lobule is the intrahepatic vein. The bile ducts are directed outwards towards the interlobular connective tissue.

supply blood to the peripheral portions of the lobule by vessels which are called interlobular veins.

In the centre of each lobule is a vein called an intrahepatic vein a number of which drain into what are called sublobular veins and a series of sublobular veins forms the hepatic veins. These vessels are not separated from the liver cells by a sheath of loose connective tissue; they cannot therefore collapse when cut across, but must remain patent.

The bile ducts arise as intracellular bulbous spaces and the bile passes along grooves between the cells so that each bile capillary lies between two cells without any definite wall. Physiologically the centre of the lobule should be the place whither the

bile ducts lead : this would correspond to an inversion of the description of the liver lobule based on the blood supply, as the bile capillaries lead to the interlobular connective tissue where the ducts are formed. The blood percolates between the liver cells in its passage from the interlobular to intralobular vessels. The endothelial covering of the liver cells is deficient and is represented by a few cells (Kupffer cells) which can take up solid particles and are frequently seen full of granules of various kinds. The blood is so intimately associated with the cells that it actually penetrates into spaces within the liver cells as can be seen in injected preparations. The liver cells contain granules, some of which can be demonstrated by specific stains, e.g. glycogen can be shown by iodine or by Best's carmine.

**Glycogenic Function of the Liver.** During absorption of carbohydrate the amount of hexoses in the portal blood is increased ; at the same time glycogen is formed in the liver. This increase in the glycogen of the liver following a meal rich in carbohydrate was observed by Claude Bernard in 1850 by treating the liver with iodine which caused the outer parts of the lobules to stain brown. After the liver is removed from an animal the glycogen disappears and is replaced by glucose. These observations led Claude Bernard to believe that the liver acts as a storehouse for carbohydrate. During absorption the excess of sugar is taken from the portal blood so that the systemic blood is not flooded with sugar through the hepatic veins.

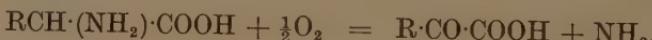
When carbohydrate is not being absorbed and the portal blood does not contain an excess of carbohydrate the glycogen is hydrolyzed so that the blood in the hepatic veins contains enough sugar to keep the supply of glucose in the systemic blood from falling to too low a level. This hypothesis has been substantiated by further work and in a later chapter we shall deal with the way in which the sugar supply can be regulated.

*Preparation of Glycogen from the Liver.* If an animal is given a diet containing a large amount of carbohydrate and is killed suddenly about four hours later a large amount of glycogen will be found in the liver. The liver must be rapidly removed and placed in boiling water containing a little acetic acid. If the liver is left the enzyme in the liver rapidly converts the glycogen into sugar. After the enzyme has been destroyed by boiling, the liver is ground up and re-extracted. The opalescent solution contains glycogen : most of the protein has been coagulated by boiling with the acidified water. The glycogen can be precipitated by alcohol added in sufficient quantity to make 60 per cent. of alcohol. For quantitative estimation of glycogen the organ is decomposed by boiling with 60 per cent. potassium hydroxide.

**Function of the Liver in relation to Amines.** The blood coming from the intestine contains products due to the digestion of proteins. These products consist partly of amino-acids and partly of ammonia. The amino-acids may pass through the liver to the systemic circulation, by which means they reach all the cells of the body which absorb them as required. Part of the amino-acids are formed into tissue proteins and part are used for energy supply. Ultimately the nitrogen of these amino-acids is passed back to the blood stream and any ammonia passed back can reach the liver by the hepatic artery.

The tissue cells and the liver deaminise amino-acids and from the ammonia set free they form urea. The liver is for its bulk more active in this respect than the rest of the tissues, so it is customary to deal with this process as a function of the liver.

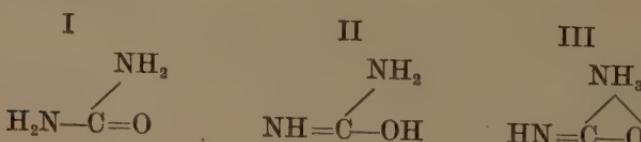
Removal of the  $\text{NH}_2$  group from amino-acids might take place either by hydrolysis giving rise to a hydroxy-acid or by oxidation giving rise to a keto-acid: the latter is the process that is believed to occur during normal metabolism.



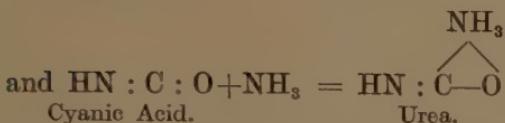
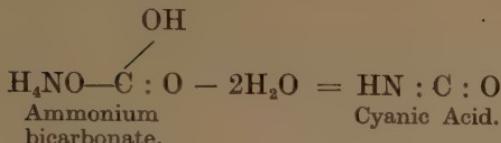
Thus the amino nitrogen of proteins can be regarded as giving rise to ammonia. In the blood there is sufficient carbonic acid to form ammonium bicarbonate with the ammonia.

The liver forms urea from ammonia. This was shown by V. Schröder, who perfused excised livers with solutions containing ammonium carbonate. He found that ammonium carbonate disappeared and the perfusion fluid coming away from the liver contained urea.

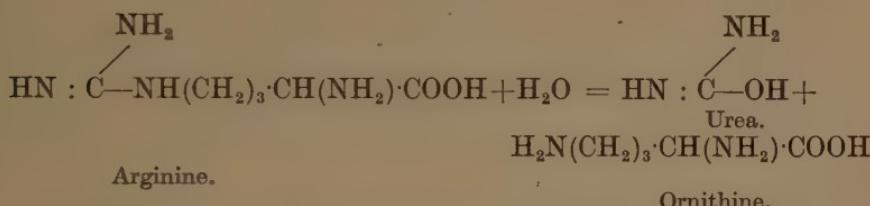
The explanation given for this reaction is that two molecules of water are removed from ammonium carbonate forming carbamide (formula I). Werner claims that urea is represented by formulae II or III. If he is correct the carbamide must pass to formula II or III by a tautomeric rearrangement or some other path of synthesis must be suggested.



Fearon has shown that urea is dissociated by urease to ammonia and cyanic acid. If synthesis of urea takes place in the reverse way it may be that cyanic acid is formed from ammonium bicarbonate by the loss of two molecules of water. In this case the synthesis can be represented by the following formulae:—



There is another source of urea but the amount formed from it is comparatively insignificant to that formed from ammonia. Arginine contains a guanidine group which can be split off by an enzyme found in the liver known as arginase, giving rise to urea and an amino-acid called ornithine.



**Metabolism of Fat in the Liver.** The liver is stated to have an influence on fat metabolism. The protoplasm of all cells contains fat held in solution so that although no fat is visible under the microscope fat can be extracted from the tissues by fat solvents. Sometimes this fat is thrown out of solution so that without an increase in the amount of fat, fat becomes visible on examination by the microscope. This is known as *fatty degeneration* in contrast with *fatty infiltration*, where fat becomes visible owing to an increased amount of fat in the tissue.

The fat obtained by extraction from a normal liver differs from that obtained from fat depôts in that it contains a larger number of unsaturated linkages. It is suggested that one of the functions of the liver is a desaturation of fats prior to their oxidation in other parts of the body. Evidence in favour of the participation of the liver in fat metabolism is shown by the changes that take place during starvation.

**STARVATION.** When an animal is kept for a short time without food the amount of glycogen in the liver is markedly reduced. After the glycogen has been reduced to a minimum, that is generally within two or three days, the liver is seen to contain fat, and by chemical analysis the actual amount of fat is increased. It is believed that this fat comes from the fat depôts as the iodine value of the liver-fat decreases, i.e. the normal liver fat is diluted by fat which is less unsaturated; more like the fat contained in the fat

depôts. This observation proves that fat is carried to the liver when the glycogen supply has been used up, but it does not show that such fat is desaturated before being sent out to other parts of the body.

Accompanying these changes in the liver, starvation causes changes in the urinary constituents and in the respiratory quotient. The intake of nitrogenous substances is abolished so that the nitrogenous excretion is the result of tissue breakdown. Under these circumstances it is found that the amount of nitrogenous constituents in the urine is diminished and the proportions of the various constituents are altered. By decreasing the amount of protein in the diet but keeping up the supply of energy by fats and carbohydrates an alteration in the proportions of the constituents derived from protein can also be shown.

After all the non-nitrogenous energy supplies have been used up the tissue proteins are used for energy and the amount of nitrogen in the urine increases. Even under these circumstances the more important organs, such as the heart and brain, are spared until the proteins of the less essential organs have been used. When the proteins of the essential organs are drawn upon to an appreciable extent death occurs : thus the increase in nitrogenous excretion in starvation is a danger signal that all the available non-nitrogenous food stores are approaching exhaustion.

That carbohydrate is used mainly in the early stages of starvation is shown by a rise in the respiratory quotient and the exhaustion of the stores of carbohydrate ; utilization of fat is shown by a fall in the respiratory quotient. A rise in respiratory quotient indicates a larger proportion of carbohydrate is being oxidized and the converse.

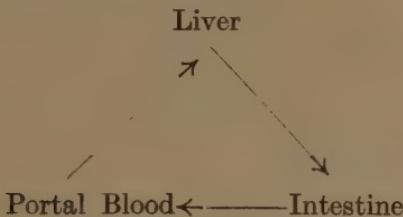
**Function of the Liver in Bile Formation.** Bile is formed by the liver cells and the bile passes by the bile canaliculi to the bile ducts. The bile as formed by the liver is altered by being passed into the gall bladder. The changes in composition are shown on p. 190.

In the gall-bladder water and salts are absorbed so that the concentrations of bile salts and bile pigments are increased.

#### *Bile Salts.*

The bile salts consist of the salts of two acids, namely glycocholic and taurocholic acids. These are formed by the union of cholic acid with glycine and taurine respectively. The liver has apparently the power to synthesize these substances, but the same acids are used over and over again. The bile acids are reabsorbed from the intestine and pass back to the liver by the portal blood for resecretion. The evidence for this reabsorption is given by experiments on dogs.

Dog's bile does not contain glycocholic acid. Glycin is present in the blood of all animals and cholic acid must be present as taurocholic acid is formed in the dog's liver, therefore the liver of the dog must lack the power of synthesizing glycocholate from glycine and cholic acid. If, however, glycocholic acid is given by the mouth to a dog glycocholate is found in the dog's bile, from which the conclusion seems justified that the bile salts are to some extent reabsorbed as such, pass to the liver and are resecreted. This is called the circulation of the bile salts.



The function of the bile salts in digestion has been described earlier (p. 190).

#### *Bile Pigments.*

Bile pigments are formed in the liver from the destruction of haemoglobin. As shown on p. 241 haemoglobin breaks up into haematin and globin : the haematin can lose iron, forming haemoporphyrin. Haemoporphyrin is allied to bile pigments. These changes are not confined to the liver as a similar series of changes can be observed in a bruise where the extravasated blood undergoes a series of colour changes somewhat resembling those which accompany the formation of bile pigment from haemoglobin.

When haematin is decomposed iron is set free, therefore one finds that the liver contains a store of iron which can be demonstrated by the use of an acid solution of potassium ferrocyanide. Conditions under which there is an excessive decomposition of haemoglobin (e.g. pernicious anaemia) cause an increase in the amount of iron in the liver. That the iron may be of use for the formation of fresh haemoglobin is indicated by the fact that the liver of the new-born child contains a large supply of iron ; this supply is required because milk is relatively deficient in iron, hence there must be sufficient of it in the liver to last over the period whilst milk is the sole food supply.

Another method whereby iron may be demonstrated histologically is to stain it with a pure solution of haematoxylin. A mordant is required for staining with haematoxylin. The iron acts as a mordant so that the iron is shown as blue stained granules.

The amount of bile pigment formed is a measure of the continuous and daily destruction of haemoglobin. If excessive breakdown of

corpuscles occurs the amount of bile formed is increased. Another consequence of a sudden breakdown of corpuscles is the passage of haemoglobin from the blood-vessels into the tissues. This would be noticed by the appearance of derivatives of haemoglobin (usually methaemoglobin) in the urine.

The sinusoids of the liver have special stellate cells lying on the surface of the liver cells. These Kupffer cells have been seen containing remnants of red blood corpuscles and they may be instrumental in collecting the haemoglobin for the formation of bile pigment.

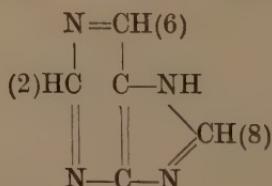
The source of the cholesterol of bile is not known. It may be the source of cholic acid which is required for the formation of bile salts.

Mucin (or nucleo-protein), soaps and lecithin, are contained in bile, but their physiological significance is not known.

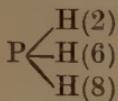
**Metabolism of Nucleo-Protein.** Nucleo-protein can be decomposed into nuclein and protein. The nuclein is hydrolyzed into protein and nucleic acid. Nucleic acid has been carefully and extensively studied and its structure and decomposition products are fairly well understood. Plant nucleic acid differs from the nucleic acid of animals mainly because it contains pentoses whilst the latter contains hexoses. Nucleic acid is decomposed by hydrolysis. The enzyme nucleinase decomposes nucleic acid into four similar nucleotides. Each of these consists of one molecule of phosphoric acid, united to a molecule of hexose and a base. The four bases in thymus nucleic acid are adenine, guanine, cytosine and thymine.

The four nucleotides are each decomposed by their own specific nucleotidase into phosphoric acid and a nucleoside (hexose + base) whilst the nucleosides are hydrolyzed by nucleosidases into carbohydrate and a base. The bases cytosine and thymine are pyrimidine derivatives and their fate in the animal body is unknown. Adenine and guanine are purine derivatives. They can be deaminised by adenase and guanase, giving rise to hypoxanthine and xanthine respectively; hypoxanthine can be oxidized to xanthine and xanthine to uric acid by xanthine oxidase.

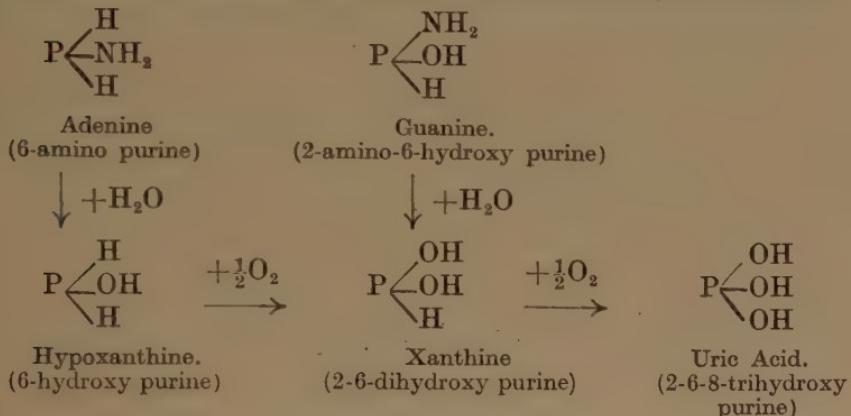
The chemical relations of these substances are best shown by their structural formulæ. If we represent purine by the formula,



the three replaceable hydrogen atoms in the positions 2, 6 and 8 are represented in the abbreviated formula,



The purine derivatives can be shown schematically as follows :—

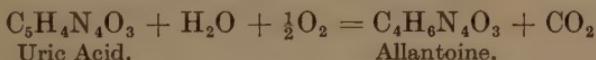


**Uric Acid.** In the formation of uric acid from the hydroxy purines the liver plays an important part. The following table from Jones shows this clearly :—

TABLE XXXVIII

| Organ Extracts which contain Xanthine-oxidase. | Organ Extracts which do not contain Xanthine-oxidase. |
|--|---|
| Human liver                                    | Other Human organs                                    |
| Ox liver                                       | Ox thymus (calf's)                                    |
| Ox spleen                                      | Pig's spleen  |
| Adult pig's liver                              | Embryo Pig's liver                                    |
| No organ of the Rat                            | All organs of the Rat                                 |

Uric acid is destroyed by an enzyme known as uricase with the formation of allantoine and carbon dioxide.



The human organism does not destroy much, if any, uric acid, hence the appearance of uric acid in the urine. Most other animals with the exception of the higher apes and Dalmatian hounds destroy uric acid so readily that only small quantities find their way into the urine.

Jones states that guanase is present in the liver, kidney and lung whilst adenase is not found in any human organs. Uricase is not present in human liver.

The statement that adinase is not found in any human organ requires further consideration. One might expect to find adenine

in human urine, but it is not present in appreciable quantities. It has been found that tissues (human and from other animals) which do not contain adinase can form hypoxanthine from combined adenine. Therefore there must be enzymes which can deaminise the purines whilst they are combined with carbohydrate, but not when they are present as free bases.

The diagram on page 275 shows the various possible ways in which uric acid can be formed from nucleic acid (Jones).

**Uric Acid Synthesis.** In birds and reptiles the chief end product of nitrogenous metabolism is uric acid. This must be synthesized from simpler substances. By perfusion experiments on the liver of birds it has been shown that uric acid may be synthesized from ammonia and lactic acid. In view of the fact that most mammals destroy uric acid in their liver this process of uric acid formation is not likely to occur in mammals.

**Other Purine Substances.** Purines in the diet are acted upon in the liver. Guanine, hypoxanthine, xanthine and nucleo-proteins will be converted into uric acid. Adenine is not acted upon by the human organism, hence if administered by the mouth or by injection it appears in the urine. Other purine substances in the food may give rise to purines in the urine. The methylpurines are partly demethylated before they appear in the urine. The following table shows the possible relation between certain methylpurines in the food and in the urine (Jones) :—

TABLE XXXIX

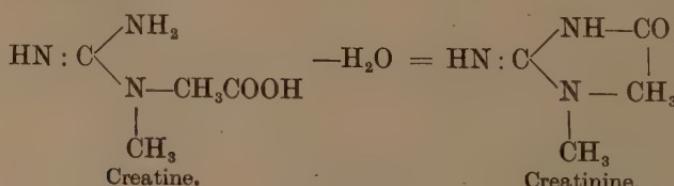
## METHYL PURINES IN THE HUMAN URINE

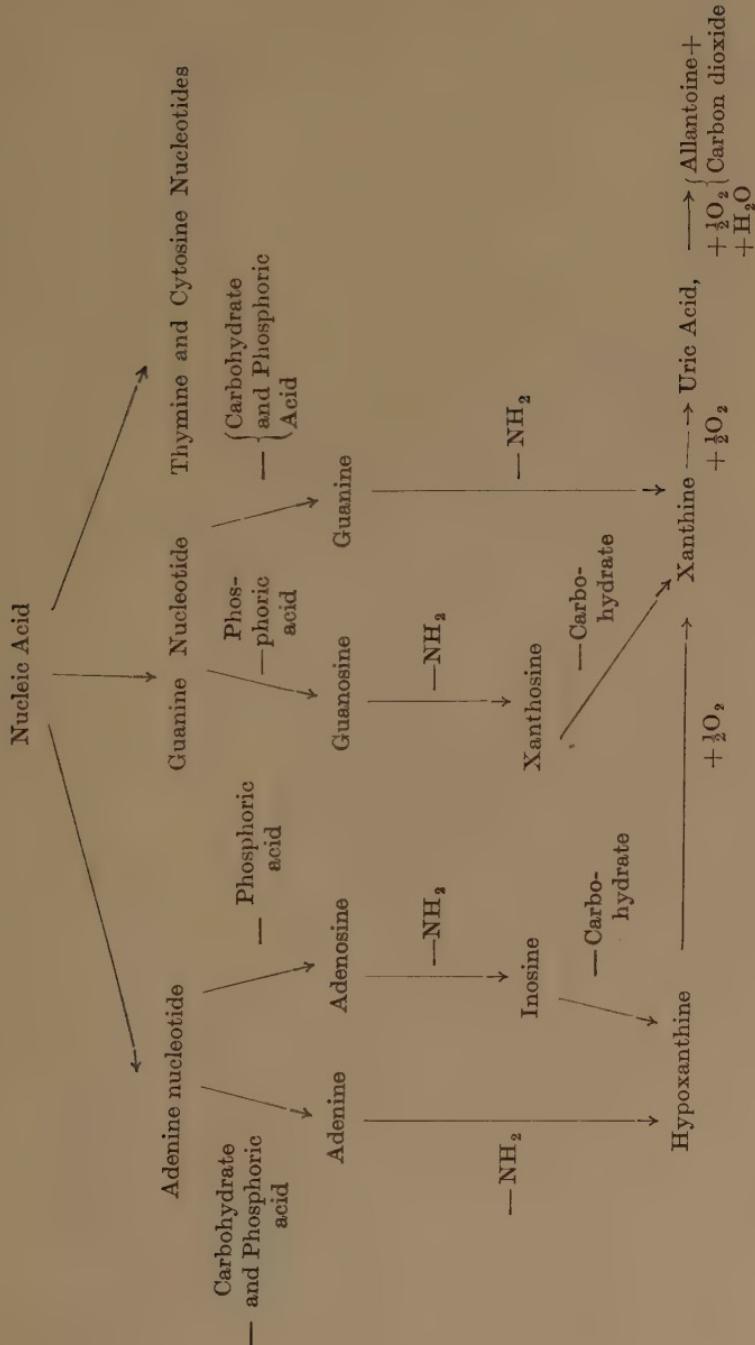
| <i>Methyl Purines of the Food.</i>    | <i>Methyl-Purines of the Urine.</i> |
|---------------------------------------|-------------------------------------|
| 1-3-7 Tri-methyl-xanthine (caffeine)  | 1-7 Di-methyl-xanthine              |
| 1-3 Di-methyl-xanthine (theophylline) | 1-methyl-xanthine                   |
| 3-7-Di-methyl-xanthine (theobromine)  | 7-methyl-xanthine                   |

It is to be noted that the methyl group in position 3 is most readily removed.

**Creatine and Creatinine.** The justification for the inclusion of these two substances is that the liver is believed to be related to their metabolism (E. Mellanby).

Creatine is converted into creatinine by dehydration, usually by heating with acid.





Creatine is found in muscle and in the liver, but it does not always appear in the urine. It may be present in the urine in childhood, during pregnancy, menstruation, starvation and various diseases.

Creatinine is found in the urine and it is constant in amount so that it is believed to represent some constant process which may be called endogenous metabolism, i.e. independent of diet, muscular exercise, etc.

Creatine may have something to do with muscle tone. Its amount in muscle increases when the muscle shows tonic contraction, but not when intermittent contractions are produced.

Creatine given by the mouth was not supposed to form creatinine but Benedict and Osterberg have recently shown that if creatine is fed to dogs for long periods of time, the amount of creatinine in the urine increases after a latent period of about a week. When creatine is given by the mouth some of it appears in the urine. It seems as if muscles can hold a certain amount of creatine. When more is provided the muscles can take up some of it but the excess appears in the urine.

When the store of creatine is increased by means of food an increased excretion of creatinine occurs which does not appear for some days, but gradually increases during the period of feeding on creatine. After the administration of creatine is stopped the creatinine excretion slowly falls to its original level.

E. Mellanby has shown in the developing chick that muscle at first contains no creatine. Later creatine appears in muscle and the amount continues to increase even after hatching. Creatine appears in the liver at the same time that it appears in muscle. The material from which creatine is formed is not known.

**The Liver as Venous Reservoir.** The liver can vary in volume, therefore it can serve as a storehouse for blood. When a large supply of blood is required for the systemic circulation the liver probably passes out some of the store of blood contained in it.

**Formation of Fibrinogen and Protective Substances.** These substances are said to be formed by the liver. As the liver is the chief metabolic organ of the body one may expect to find that it plays a prominent part in all general chemical processes. Its intimate relation to the blood and the large amount of blood flowing through the liver are a necessary factor for the transport of material to and from this important metabolic organ. If any of the processes are exothermic then the liver may be looked upon as one of the sources of heat in the body.

**Formation of Red Blood Corpuscles in the Fœtus.** This function will be discussed in relation to the development of the body (see p. 574).

## THE SPLEEN

Associated with the liver is the spleen; the link between these two organs is that the splenic vein unites with the superior mesenteric vein to form the portal vein.

The structure of the spleen is that of a haemolymph gland and it may participate with the other lymph organs in the formation of white blood corpuscles. In the foetus it may assist in the formation of red blood corpuscles. For these functions a later section must be consulted (Chapter XLIV). The spleen is surrounded by a muscular capsule and it shows rhythmical changes in volume. The variability in volume may allow it to act as a reservoir, but the actual changes in volume are too small to make any appreciable difference.

**Structure.** Trabeculae penetrate from the capsule into the parenchyma of the spleen. The splenic artery enters at the hilus and the larger arteries pass inwards in branches of the trabeculae. The veins accompany the arteries in their course. The arterioles leave the trabeculae after which they become surrounded by masses of lymphocytes forming the Malpighian corpuscles. The Malpighian corpuscles are therefore lymph nodules which contain arterioles. The blood finally flows into the spleen pulp and after percolating through the pulp it reaches the splenic veins.

The spleen pulp consists of a reticulum containing lymphocytes and leucocytes as well as red blood cells. The leucocytes are largely of the mononuclear or transitional variety, but there are also some multinucleated giant cells.

In the spleen may be found fragments of red blood corpuscles



FIG. 132.—Photomicrograph of Malpighian Corpuscle of Spleen ( $\times 88$ ).

Note oval collection of cells surrounding small artery.

and an excess of iron-containing substances, and it is thought that the spleen has some activity in destroying damaged red blood corpuscles thus liberating the haemoglobin so that the liver may decompose it forming the iron-free residue of haematin into bile pigments. In favour of this view it has been claimed that the plasma in the splenic vein contains a larger amount of free haemoglobin than is found in the blood in other veins. In pernicious anaemia iron accumulates in the spleen in a similar way to which it accumulates in the liver.

Like lymph glands the spleen may act as a filter. Solid particles such as micro-organisms may accumulate in the spleen, and this may be one of the places in which they are destroyed.

The presence of numerous extractives suggests that some chemical processes occur in the spleen. Extracts of this organ are, however, without action on the various stages of purine metabolism.

### Lymphoid Organs

Associated with the lymphatic system are a series of organs containing what is known as lymphoid tissue. Lymphoid tissue consists of a delicate supporting network of connective tissue forming a reticulum. In the reticulum are packed innumerable small round cells or lymphocytes. The cells seem to grow in masses.

A *lymphatic gland* is surrounded by a capsule from which trabeculae pass into the gland to convey blood-vessels. Near the capsule the lymphocytes are collected into nodules to form a cortical portion. The central portion of the gland or medulla is more open, forming lymph paths. The lymph enters at the convex surface of the gland, flows through channels lying alongside the capsule and trabeculae to reach the lymph-paths of the medulla. The lymph drains away at the hilus.

In the *tonsil* the lymphoid tissue lies below a stratified epithelium and crypts lined by stratified epithelium penetrate into the substance of the tonsil.

In the *intestine* lymphoid tissue may be found amongst the various structures forming the mucous membrane, generally as isolated masses.

The *thymus* was originally a glandular structure developed from the alimentary canal. The gland is divided into lobules by connective tissue. The remnants of the ducts are said to persist as nests of epithelioid cells known as Hassal's corpuscles.

Sometimes blood mixes with the lymphoid structure. This mixture of blood and lymphoid tissue is seen in *haemo-lymph* glands. A special example of such an organ is the spleen.

## CHAPTER XXI

### ABSORPTION, EXCRETION, SECRETION AND MUSCULAR CONTRACTION

The various processes to be discussed in this chapter are described together because they must be discussed in relation to the conversion of one form of energy into another. As mentioned on page 107, the First Law of Thermodynamics is that energy is neither created nor destroyed, and the Second Law is that although other forms of energy can be quantitatively converted into heat, heat can only be converted into work under certain conditions. In order to convert heat into work there must be a supply of heat at a higher temperature which can be transferred to a lower temperature. In carrying out such a process the efficiency of the transformation is the ratio of the amount of energy turned into external work to the total energy used.

Efficiency  $A/Q = (T_1 - T_2)/T_1$ , where  $A$  = external work accomplished,  $Q$  = total energy expended as heat,  $T_1$  and  $T_2$  are the absolute temperatures of the original and final conditions.

Later in this chapter we shall have to return to this point in relation to contraction of muscle.

#### Transformation of Energy Potential

Many processes in the body are accompanied by a transformation of energy potential. That is a certain amount of energy, e.g. the potential energy of carbon compounds, is used to increase the potential of some other form of energy, e.g. increase in osmotic or hydrostatic pressure. We do not know the mechanism by which this transformation is accomplished, but the machine is the living cell. The cell plays the same part that an electric motor does when it transforms electrical energy into kinetic energy (Moore). The efficiency of such a transformation is generally greater when the energy does not pass through the form of heat and the cell seems to avoid this path of transformation. The problems concerned in transformation of energy occur in all branches of physiology. It is considered advisable to discuss them here by using several examples of physiological processes. By dealing with them in the same chapter repetition of the same discussion is avoided.

The processes of absorption, excretion and secretion deal with the transfer of chemical materials. One frequently hears a distinction made between physico-chemical and so-called "vital" processes. By physico-chemical processes one must understand some process which depends in a purely passive way on differences in potential of energy whilst by "vital" process one may understand either something which is independent of the laws of thermodynamics or merely the regulation by which one form of energy is converted into another. Nowadays no one believes that any vital processes are independent of the laws of thermodynamics, therefore in what follows we shall endeavour to distinguish between those processes which occur as the result of a running down of potential of one form of energy and those which consist of the transformation of one form of energy into another. Linked processes whereby a transformation of energy may occur are known outside the living cell : thus there is no clear distinction between vital and non-vital processes.

**Influence of Activity on Metabolism.** When a muscle becomes active it uses a larger amount of oxygen than when at rest : activity of other tissues is also accompanied by an increased use of oxygen. If the nerve to the salivary gland is stimulated in addition to secreting saliva it uses more oxygen.

The amount of gas exchange is measured by the volume of blood flowing through the organ multiplied by the difference in concentration of gases in the arterial and venous blood entering and leaving the organ. Sometimes the increase in circulation is so great that the venous blood is less different than usual from the arterial blood, yet the total volume of gases exchanged is greater than when the organ is at rest. Some typical examples of the effect of activity on the gas exchange are given in Table XL.

TABLE XL  
EFFECT OF ACTIVITY ON GAS EXCHANGE IN C.C. PER MINUTE

| Per gram of—               | Resting.                 |                            | Active.                  |                            |
|----------------------------|--------------------------|----------------------------|--------------------------|----------------------------|
|                            | O <sub>2</sub> absorbed. | CO <sub>2</sub> given out. | O <sub>2</sub> absorbed. | CO <sub>2</sub> given out. |
| Muscle . . . .             | 0.0028                   | 0.0026                     | 0.010                    | 0.013                      |
| Kidney . . . .             | 1.66                     | —                          | 5.58                     | —                          |
| Submaxillary Gland . . . . | 0.32                     | 0.20                       | 1.20                     | 1.58                       |
| Pancreas . . . .           | 0.49                     | —                          | 1.71                     | —                          |

**Diffusion Pressure.** The driving force for the running down of osmotic energy may be called the diffusion pressure (Haldane). It is measured by a coefficient which is defined as the amount of substance passing through the unit area of one square centimetre in unit time when the difference of concentration is unity, e.g. 1 cm. of distance. A difference of concentration of unity over a

distance of 2 cms. would give only half the driving force, that is the gradient of pressure depends on the difference of pressure divided by the distance apart at which the two pressures are measured.

If a semi-permeable membrane is interposed the solvent passes through to dilute the solute. Diffusion can therefore be looked upon as a movement of the solute in one direction and a movement of the solvent in the other direction ; the driving force depending upon differences in concentration of the solute.

### ABSORPTION

**Gas Exchange in the Lungs.** The exchange here is the passage of oxygen from the alveolar air to the blood and the passage of carbon dioxide from the blood to the alveolar air.

In Fig. 120, the pressures of oxygen and carbon dioxide are represented as being the same in alveolar air and arterial blood. If the exchange is due to diffusion there must be some slight difference of pressure between the two..

The problem to be discussed here is the amounts of oxygen and carbon dioxide which can pass through the lung in a given time. Carbon dioxide diffuses more rapidly than oxygen, hence a lower difference of pressure would drive the same amount of carbon dioxide through the lungs. Fig. 120 does show that the difference of pressure is less for carbon dioxide than for oxygen.

One must always remember that with short distances such as those of cellular dimensions diffusion becomes very rapid (Graham). A difference of pressure of 1 mm. Hg between the alveolar air and the blood must be considered in relation to the distance between the blood and air. If the distance be taken as five micra the corresponding difference of pressure over the standard distance of 1 cm. would be 2,000 mm. or almost three atmospheres. The total surface of the alveoli of the lung has been stated to be about 90 square metres. When one considers these figures it seems probable that diffusion can account for the exchange of gas in the lungs. The driving force must be the difference of pressure between the layer of air in contact with the alveolar epithelium and the plasma in contact with the capillary wall.

The driving force for gas diffusion is the pressure of the gas. In gas analyses the pressure is determined by the percentage concentration multiplied by the total pressure in the gas space. In solution it is not necessarily the total volume of gas in solution which is important, but the pressure of the gas. The pressure is that measured by the partial pressure of the same gas in the space above when the liquid and gas are in equilibrium.

Unfortunately measurements of gas concentrations in alveolar air give only the average composition of air coming from the

infundibula and alveoli. The actual concentrations in the layer of air in contact with the alveoli will depend upon the adequacy of mixing. Similarly the analysis of blood does not tell us the actual pressures in the layer of plasma in contact with the capillary wall. The differences in pressure must be less than those found by analyses of alveolar air and whole blood, but we do not know whether the true pressures would make any significant difference to the process of diffusion.

Most physiologists acknowledge that gas exchange during sedentary conditions may be merely a matter of diffusion, but some are not satisfied that sufficient gas can pass through to account for the gas exchange during severe muscular work (Haldane). If it can be shown that more gas passes through than can be accounted for by diffusion then a transformation of energy or secretion must occur. If the pressure of oxygen can be shown to be greater in the blood than in the lungs or the carbon dioxide pressure to be less in the blood than in the lungs, then secretion must occur. Secretion of gas is not impossible as the oxygen pressure in the swim bladder of a fish is frequently much greater than the oxygen pressure in the water surrounding the fish. This secretion is controlled by the vagi. There is, however, a special secretory gland, whilst in the lung the cells are reduced to the thinnest possible layer.

**Absorption from the Intestine.** Here we have a condition in which the concentration of substances in the intestine tends to increase during digestion and to remain at a uniform low level in the blood. The surface of the intestine is greatly increased by the presence of villi and substances absorbed into the blood are rapidly removed from it so that the blood coming to the intestine is not loaded with the substances which were absorbed during a previous passage through the capillaries of the intestinal villi.

The cells of the intestine are columnar, therefore the conditions are not so favourable to diffusion as the cells of the lung. The gradient of pressure is less because of the greater distance between the two sides of the membrane formed by the cells. On the other hand if an increase of energy potential is brought about by a cell the greater the thickness of the cell the less the work required from the cell per unit volume of protoplasm. The separation of substances from solutions in the body may be regarded as a process whereby the pressure of a substance is maintained low at one side so that material will pass from the surroundings into the cell and maintained high at the other side so that the same substance will diffuse out from the cell on that side. The work done is in maintaining this difference of concentration and more work per unit volume of cell will be required when the gradient is steep. Hence columnar cells are more suitable than flat cells for secretion.

The great difficulty is to obtain exact experimental evidence on absorption. Salt solutions more concentrated than blood plasma can be absorbed, but that may be the result of the osmotic pressure of the serum proteins (Starling). As the proteins cannot pass through the membrane a permanent diffusion potential exists which may counterbalance an apparent difference in the opposite direction. As inorganic salts can pass through the membrane their osmotic action is less effective. Anomalous osmosis, or the condition in which a greater concentration of salt passes through at the beginning of osmosis, does not make a greater total pressure on the side to which the salt is diffusing.

*Absorption of an Animal's own Serum.* The serum of an animal placed in its intestine can be absorbed. This suggests some cellular activity, but we do not know to what extent the serum differs from the blood plasma due either to the process of coagulation or to changes which occur in the intestine. The positive value of this experiment is of more importance than the objections to it based on the possible changes in composition of the serum. The intestinal loop in which the serum had been placed was previously well washed to remove trypsin and other enzymes.

*Removal of the Epithelial Layer.* The epithelial cells of the intestine may be removed by poisoning them with 0·1 per cent. sodium fluoride or by killing them by temporary arrest of the circulation. The rate of absorption is decreased by the removal of the cells. Physically the rate of diffusion ought to be increased because the distance between the blood-vessels and intestinal contents is decreased by the removal of the cells (Reid). The objection to this experiment is that the fluoride may have altered the physical condition of the part of the intestinal wall left after removing the cells. Therefore the delay in absorption may be due to the passage through a membrane of different physical properties. In this case the positive results obtained are also of more importance than objections based on the suggested physical alterations to the intestinal wall.

*Differential Absorption of Hexoses.* Hewitt has shown that if equivalent concentrations of glucose, fructose and galactose are placed in a loop of the small intestine the glucose is absorbed more rapidly than galactose and the latter more rapidly than fructose. This result cannot be explained by diffusion or osmosis and after the epithelium of the intestine has been destroyed all three sugars are absorbed at the same rate.

*Gas Exchange during Absorption.* During absorption from the intestine the amounts of oxygen taken in and of carbon dioxide given off are increased above the resting values. Some of this increase may be due to other activities of the intestine (movements,

etc.), but it is significant that there is an energy exchange occurring which could be used to facilitate absorption (Brodie, Cullis and Halliburton). These various experiments suggest that absorption is not purely a matter of diffusion but is accompanied by a transfer of energy potential from one form to another.

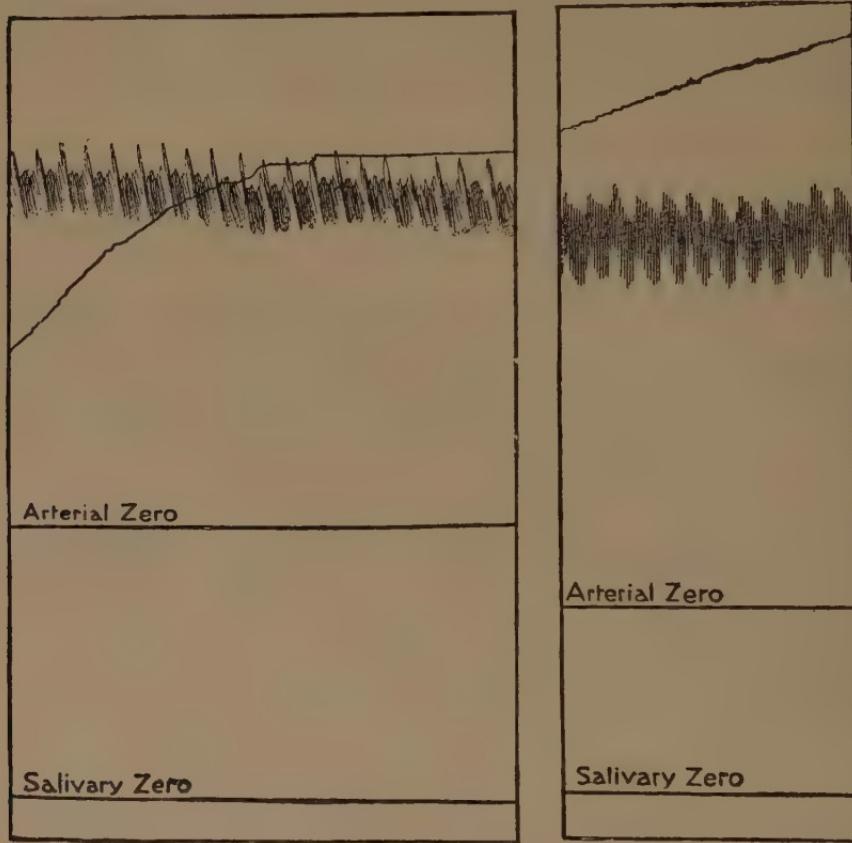


FIG. 133.—Tracings from Two Different Dogs, anæsthetized by Morphine and Chloroform, showing the Arterial (Carotid) Blood Pressures and the Secretory Pressures of Saliva during Excitation of the Chorda Tympani Nerve (L. Hill, from *Proceedings of the Royal Society*).

With a salivary pressure of 240 mm. Hg and an arterial pressure of 130 mm. Hg, blood still flowed through the gland, therefore the gland tubules are prevented from pressing on the blood-vessels by the inextensible basement membrane.

### SECRETION

**Secretion by the Salivary Gland.** If a cannula is tied into the duct of the submaxillary gland and the nerve to it stimulated the pressure in the duct may rise to double that of the arterial pressure (Ludwig). This can be explained only by a pumping action of the gland. There has not been demonstrated any constituent in

the saliva which will cause sufficient osmotic pressure to produce this rise of pressure.

Accompanying this rise of pressure there is an increased gas exchange, an increased blood flow, and an electrical change. The first of these can furnish the energy by which the cell is able to produce the rise of pressure. As the pressure in the duct is so great one would expect the gland cells to be pressed outwards so as to compress the blood-vessels and stop the blood flow. The basement membrane is probably responsible for preventing the blood-vessels from being occluded by the salivary pressure (L. Hill).

**Secretion of Hydrochloric Acid.** This is an example of another process which requires a transformation of one form of energy to another. The concentration of hydrogen ions in the blood is less than  $1 \times 10^{-7}$  N. The concentration of hydrogen ions in the gastric juice is more than  $5 \times 10^{-2}$  N. Therefore the concentration of these ions has been increased  $5 \times 10^5$  or about half a million times. No matter what intermediate steps occur the energy required for this process is the same and this is shown by the formula on page 286.

### EXCRETION

**Formation of Urine.** This is a problem which has given rise to a great deal of experimental work and discussion. From the previous examples given the student will see that energy potential must be available whenever a substance is concentrated in passing from one place to another, or if it is passed along at a greater rate than can be accounted for by the process of diffusion. In the kidney such increase in concentration is accomplished. This is evident when one compares the concentrations of various substances in the blood plasma and urine.

TABLE XLI

CONCENTRATING ACTION OF THE HUMAN KIDNEY (MODIFIED FROM CUSHNY)

|                                       | Blood plasma.<br>per cent. | Urine.<br>per cent. | Increase in Concen-<br>tration produced<br>by Kidney. |
|---------------------------------------|----------------------------|---------------------|---|
| Water . . . . .                       | 90-93                      | 95                  | $\times 1.05$   |
| Proteins, fats and colloids . . . . . | 7-9                        | 0.0                 | $\pm \infty$  |
| Dextrose . . . . .                    | 0.1                        | —                   | —   |
| Urea . . . . .                        | 0.03                       | 2.0                 | $\times 60$   |
| Uric Acid . . . . .                   | 0.002                      | 0.05                | $\times 25$   |
| Sodium ions . . . . .                 | 0.32                       | 0.35                | $\times 1$  |
| Potassium , , . . .                   | 0.02                       | 0.15                | $\times 7$  |
| Ammonium , , . . .                    | 0.001                      | 0.04                | $\times 40$   |
| Calcium , , . . .                     | 0.008                      | 0.015               | $\times 2$  |
| Magnesium , , . . .                   | 0.0025                     | 0.006               | $\times 2$  |
| Chlorine , , . . .                    | 0.37                       | 0.6                 | $\times 2$  |
| Phosphate , , . . .                   | 0.009                      | 0.27                | $\times 30$   |
| Sulphate , , . . .                    | 0.003                      | 0.18                | $\times 60$   |

It is quite evident from Table XLI that there must be a decrease of some form of energy potential to balance the increases in concentration brought about in the formation of urine. In what follows we will endeavour to find out which part of the kidney is responsible for producing the increases in concentration of the various constituents, and whether the concentration is accomplished by absorption of solvent.

The least amount of work done in forming a litre of urine is given by the formula :—

$$A = RT \left[ \sum \left( C_u \log \frac{C_u}{C_b} \right) + \sum C_b - \sum C_u \right]$$

In which  $A$  = the work done,  $RT$  = the gas constant,  $C_b$  = molecular concentration of a given substance in the blood,  $C_u$  = molecular concentration of the same substance in the urine and  $\Sigma$  indicates that the total is made up of the sum of the similar terms for each separate constituent or solute.

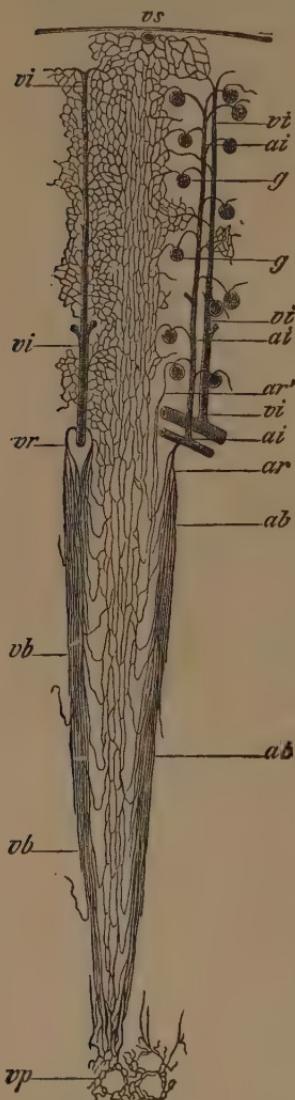
**Structure of Kidney.** The kidney consists of a number of long tubules each beginning in a dilated extremity formed by a thin-walled capsule situated in the cortex of the kidney (Bowman's capsule). The capsule has become invaginated to contain a tuft of blood capillaries called a glomerulus. The whole structure is called a Malpighian corpuscle. The tuft of blood-vessels arises from an artery given off directly from the arches of blood-vessels which run between the cortex and medulla of the kidney.

The capillary tuft is peculiar in that it consists of a series of parallel loops and the emergent vein is narrower than the arteriole entering it.

FIG. 134.—Diagram of Distribution of Blood-vessels in Human Kidney (Ludwig).

*ai*, interlobular arteries; *vi*, interlobular veins; *g*, glomerulus; *vs*, stellate vein; *ar*, *vr*, arteriae and venae rectae, forming bundles; *ab*, *vb*, *vp*, venous plexus in the papillæ.

To the thin-walled capsule is connected, through a neck, a convoluted tubule lined by cubical cells



(first convoluted tubule). This is succeeded by a thin-walled tube which bends down towards the medulla, forming a U-shaped bend (loop of Henle).

The walls of the ascending limb are thicker than those of the descending limb.

When the ascending limb reaches the cortex it forms a zig-zag tubule consisting of cubical cells. The zig-zag tubule is continued as a straight or junctional tubule which runs into a collecting tubule running inwards towards the medulla of the kidney. Several collecting tubules unite to form a duct of Bellini which opens on the surface of a pyramid into the pelvis of the kidney.

The blood-vessels from the glomerula (*vasa efferentia*) break up into a second set of capillaries surrounding the tubules. In the frog this second set of capillaries is joined by branches from the renal portal vein which

bring blood from the anterior abdominal vein up to the kidney. In the mammal the capillaries surrounding the tubules may receive blood which has not passed through the glomeruli.

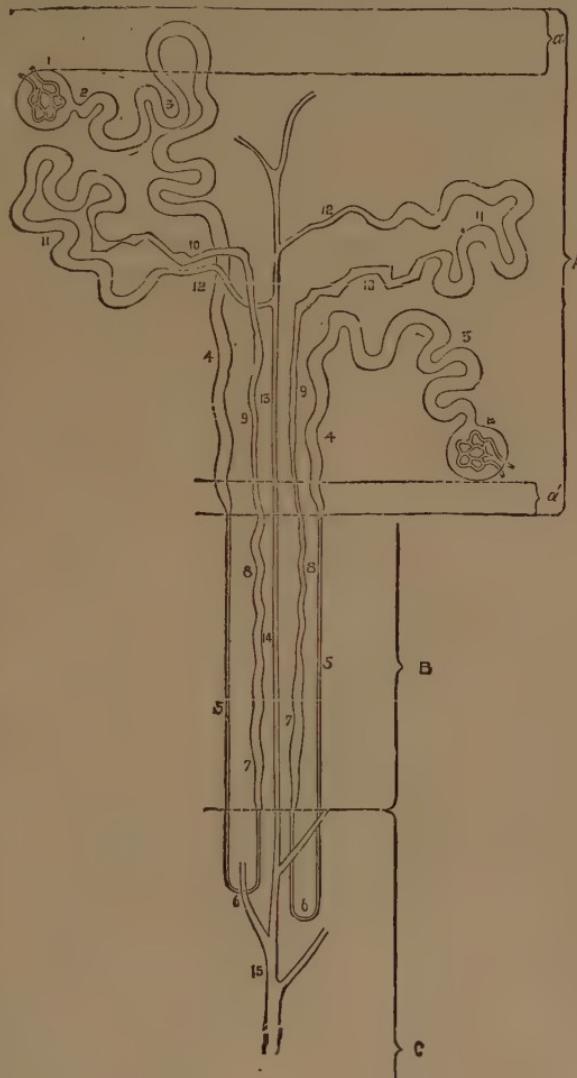


FIG. 135.—Diagram of Course of two Uriniferous Tubules (Klein).

A = cortex, B = boundary zone, C = papillary tissue of medulla, a, a' = superficial and deep layers of cortex free from glomeruli, 1 = Bowman's capsule containing glomerulus, 2 = neck, 3 = proximal convoluted tubule, 4 = spiral tubule, 5 = descending limb, 7 and 8 = ascending limb of loop of Henle, 9 10 and 11 = distal convoluted tubule, 12 = junctional tubule, 13 and 14 = collecting tubule, 15 = duct of Bellini.

This complicated structure suggests that formation of urine takes place by a series of processes. It is customary to contrast the functions of the glomeruli and the tubules, but it may be possible at a future date to distinguish between the various parts of the tubule. The straight and collecting tubules probably serve only as conducting tubes.

**Functions of the Glomeruli.** The glomeruli are believed to be filtering organs. The afferent blood vessels are muscular tubes which open suddenly into a large area of parallel capillary loops. The velocity of the blood will be suddenly decreased, hence, according to Bernoulli's theorem (see p. 77), the lateral pressure in the capillaries may be greater than in the entering vessel. The pressure is maintained because the narrower vasa efferentia prevent a free flow of blood away from the glomeruli. The walls of Bowman's capsule are thin and as the capillary walls are also thin the conditions are those which would favour a physical process such as filtration.

The process of filtration is antagonized by the osmotic pressure due to those substances which cannot pass through Bowman's capsule (proteins). As measured by Starling the proteins give a pressure of about forty millimetres of mercury. The formation of urine stops when the arterial blood pressure falls to about sixty millimetres, but if the colloids of the blood are diluted by removal of blood from an animal and reinjection of the corpuscles suspended in saline, formation of urine may occur at a lower blood pressure. If the effective osmotic pressure is decreased filtration will occur at a lower pressure, hence the formation of urine at a lower blood pressure when the proteins are diluted.

*Influence of Blood Flow on Glomerular Action.* If the blood flow is stopped the flow of urine ceases. Therefore filtration is not the only factor in the action of the glomeruli. The cells are affected by lack of oxygen, thus their permeability may be altered. Increased blood flow causes an increased passage of liquid through Bowman's capsule. This is what one would expect because of the conversion of the kinetic energy into pressure according to Bernoulli's theorem. The pressure and flow of blood through the glomeruli does not depend entirely on the systemic blood pressure. Constriction of the afferent blood-vessels will tend to cause a fall of pressure in the glomeruli, whilst constriction of the efferent vessels will tend to cause a rise of pressure. Dilatation of the vessels would lead to the opposite effect. We may expect to find that constriction of afferent vessels is accompanied by dilatation of efferent ones and the reverse.

In this way the pressure in the glomeruli may be regulated from a low pressure up to that of the arterial pressure apart from any influence due to the conversion of kinetic energy into pressure.

The cells of Bowman's capsule may possess some selective activity. It has been found that during perfusion of the frog's glomeruli glucose will be found in the urine. By increasing the amount of sodium bicarbonate in the perfusing fluid glucose will no longer pass through Bowman's capsule. The relative amounts of calcium and potassium also affect the permeability for glucose (Hamburger).

**Function of the Kidney Tubules.** As mentioned above different parts of the tubule may have different functions, but the discussion of the function of the tubules is usually limited as to whether they absorb or excrete.

We may look upon the tubule cells as having the power of converting the potential energy of food materials into osmotic energy as represented by an increased concentration. By the process of diffusion solute moves from the area where the concentration is high to where it is low, whilst water moves in the reverse direction. There is no reason to suppose that in living cells the movement in opposite directions of water and solute molecules is dissociated. If the cell reverses the direction of diffusion it probably reverses both the current of solute and of solvent. The net result is that the side of the cell next to the blood stream has a low concentration of a certain solute. Hence that solute will diffuse from the blood into the cell. The diffusion of water will not be governed by the concentration of only one constituent, but by the total difference in molecular concentrations, but according to Table XLI the total concentration in urine is much greater than that in blood. The extent to which the blood is deprived of any particular solute will depend on the difference of diffusion potential and the length of time that the blood takes in passing through the capillaries in contact with the cells. In any case the blood will not be deprived of the *whole* of any given solute. The side of the cell next to the lumen of the tubule has a high concentration of solute, hence the solute will diffuse into the lumen and water into the cell. Absorption and excretion are therefore complementary. The extent to which they occur will depend upon the activity of the cell. The thicker the cell the less the gradient between the two sides of the cell and the easier for the cell to maintain the difference. In other words the energy expenditure per unit mass of protoplasm will be less.

#### THEORIES OF URINE FORMATION.

Bowman in 1840 suggested that the urine had a double origin. He believed that the water and salts were filtered through the capsule whilst the organic materials were added by the tubules.

Ludwig's opinion (1844) was that the glomerulus formed a dilute filtrate of all the urinary constituents and that these became concentrated by absorption of water in the tubules. As both views require the expenditure of energy by the cells, there is nothing to choose between them from a physico-chemical point of view.

Cushney's (1917) so-called "modern" view is merely Ludwig's hypothesis, with the addition that ideal Ringer-Locke solution is absorbed from the tubule.

*Experimental Evidence of the Functions of the Tubule.* There is a certain amount of evidence that the function of the tubule differs from that of the glomerulus. If a free flow of very dilute urine is produced by the injection of sodium chloride or Ringer solution there is no increase in the amount of oxygen used by the kidney. This is the sort of result to be expected in a process of filtration where the energy supply is the blood pressure, dependent therefore on the activity of the heart.

If, on the other hand, diuresis is produced by the injection of urea, caffeine or sodium sulphate, an increased consumption of oxygen occurs (Barcroft and Straub, 1910). This points to cellular activity in concentrating urea and other organic substances, but it does not show whether the concentration is by reabsorption of water or excretion of substrate. In the experiments on frogs which Nussbaum performed in 1878 he ligatured the renal arteries, then demonstrated by subsequent injection that all the glomeruli were deprived of their blood supply. Injection of urea into these animals caused formation of urine. The results were not entirely satisfactory because the renal epithelium was destroyed. Later experiments by Beddard and Bainbridge carried out in an atmosphere of oxygen gave concordant results showing a formation of urine. Frogs can respire through their skin, hence the blood coming from the limbs was not deoxygenated and the blood passing to the tubules by the renal portal system contained enough oxygen to keep the cells alive. Formation of urine can therefore occur although the blood supply to the glomeruli is cut off.

Another important experimental procedure is that of O'Connor and Conway (1922). They calculated from histological data the cubic capacity of the tubules in the rabbit's kidneys, and found it to be approximately 120 cu. mm. for one kidney. They injected into the blood such substances as sodium chloride, uric acid and potassium iodide. The urine was collected in small quantities and the volume noted when an increase in the concentration of the injected substance occurred. With sodium chloride the results varied, on the whole it seemed to come from Bowman's capsule. Uric acid showed an increase in concentration in most experiments when about 30 to 60 cu. mm. of urine had been collected. Such a

result would correspond to an excretion by the second convoluted tubule as the volume of liquid passed before the increase in concentration occurred was less than half the total volume of the tubules up to Bowman's capsules. Potassium iodide appeared after a larger volume of urine had been obtained : thus it is excreted higher up than the uric acid, possibly from the glomerulus.

Further evidence as to the functions of the tubules is furnished by experiments in which dyes are injected into the circulation. The colour is more evident in the tubules than in the glomeruli, but this result may be due either to excretion of dye or absorption of water by the tubules. Crystals of uric acid and other substances are sometimes seen in the tubule cells. These deposits suggest that these substances are concentrated by the cells of the tubules, but it has been stated that these deposits have reached the cells by being formed in the tubule, and by penetrating the cells mechanically : such mechanical penetration seems improbable.

The formation of urine is probably the result of—

(1) Filtration through the glomerulus. This may be selective and variable in action. If the permeability of the membrane alters, the composition of the glomerular filtrate will alter.

(2) Activity of the tubule. As pointed out above, absorption and excretion are reciprocal, but the experiments by Nussbaum's method and by the method of O'Connor and Conway indicate that excretion does occur. The activity of the tubule cells will alter from time to time and their activity is accompanied by an increased oxidation.

If filtration occurs at the glomerulus the plasma flowing through the vasa efferentia will be more concentrated in colloids than normal plasma. The blood pressure will be lower in the capillaries of the tubule than in the glomerulus and the increased osmotic pressure may aid the absorption of water from the tubules, but a purely physical process such as that cannot account for the whole of the process of urine concentration.

### MUSCLE CONTRACTION

The mechanical, thermal and electrical changes which take place in a muscle when it contracts were described in Chapters II and III. Accompanying contraction in the intact animal changes in the circulation (see p. 474), and the following chemical changes also occur.

The chemical changes are—

1. Increased taking in of oxygen.
2. Increased giving off of carbon dioxide.

3. Formation of acid.
4. Diminution in amount of carbohydrate.

1. *Respiratory Exchanges in Muscle.* The gas exchange in a muscle with a circulation of blood through it is measured by multiplying the difference in the gases of the arterial and venous blood as determined by blood gas analysis by the rate of blood flow.

Muscle may also be investigated when removed from the animal and the gas exchange measured by the changes in the gas surrounding the muscle.

If a frog's muscle is kept in an atmosphere free from oxygen it will still give off carbon dioxide. This carbon dioxide arises from the carbonates of the muscle as the carbonic acid is replaced from the base by lactic acid (Fletcher). As described earlier (p. 38) contraction of muscle in an atmosphere of nitrogen is not followed by a delayed heat production, but carbon dioxide is still given off.

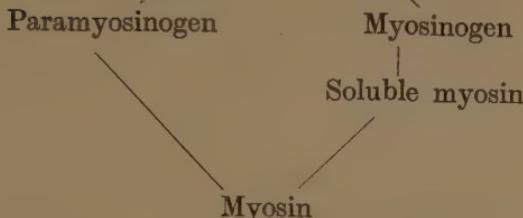
3. *Acid Production in Muscle.* An excised muscle dies and becomes acid. If a muscle is stimulated for a long period it becomes acid. If an indicator such as acid fuchsin is injected into a pithed frog, and some hours later the nerve to one hind limb is stimulated until the muscles are fatigued, the muscles of the stimulated leg will become red, showing the production of acid. The muscles become acid more rapidly if kept in an atmosphere free from oxygen, and in an atmosphere of oxygen the acid production is retarded. Hopkins and Fletcher (1906) showed that lactic acid is produced in fatigued or injured muscles, whilst keeping the muscles in an atmosphere of oxygen caused a removal of lactic acid.

It seems probable that lactic acid may be produced during the stage of contraction of muscle and removed during the stage of recovery. The early stage of heat production corresponds to the formation of lactic acid and the later stage corresponds to its removal. It has been estimated that the heat production corresponds to an oxidation of only about one sixth of the acid formed, hence most of the acid must be reformed into a precursor and not oxidized (Meyerhoff).

**Composition of Muscle.** If we wish to discover the source from which lactic acid is produced we must study the chemical composition of muscle.

Halliburton has minced muscle and squeezed out the muscle juice by an hydraulic press. The juice so obtained coagulates, giving a solid protein coagulum called myosin. The liquid portion is called muscle serum. Coagulation is delayed by cold, strong solutions of neutral salts and oxalates. The substance from which myosin is formed is myosinogen. Diagrammatically the process of coagulation can be represented thus (Halliburton) :—

## Proteins of intact muscle (mammal)



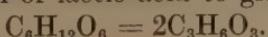
Paramyosinogen and myosinogen are globulins found in muscle plasma in the proportion of 1:4. Paramyosinogen coagulates at 47° C. and passes directly into myosin. Myosinogen coagulates at 56° C. During coagulation it passes through the form of soluble myosin which coagulates at 40° C. Soluble myosin is present as such in amphibian muscle.

TABLE XLII  
COMPOSITION OF HUMAN MUSCLE (HALLIBURTON)

|                 |   |   |   |   |   |   |       | per cent. |
|-----------------|---|---|---|---|---|---|-------|-----------|
| Water           | . | . | . | . | . | . | 73.5  |           |
| Solids          | . | . | . | . | . | . | 26.5  | ,         |
| Protein         | . | . | . | . | . | . | 18.02 | ,         |
| Gelatin         | . | . | . | . | . | . | 1.99  | ,         |
| Fat             | . | . | . | . | . | . | 2.27  | ,         |
| Extractives     | . | . | . | . | . | . | 0.22  | ,         |
| Inorganic salts | . | . | . | . | . | . | 3.12  | ,         |

**Source of Energy for Muscle Contraction.** The material oxidized can be determined by the respiratory quotient (see p. 210). In the intact organism the respiratory quotient depends upon the nature of the diet. With heavy muscular exercise the respiratory quotient rises slightly at first and shows a slight fall afterwards. This suggests combustion of more carbohydrate during exercise, and that afterwards less carbohydrate is left to be oxidized, so the respiratory quotient falls until the normal balance is restored. Hard muscular work is not accompanied by any marked excretion of nitrogenous substances, hence the energy for muscle contraction is not derived from oxidation of amino-acids or other nitrogenous substances. A slight wear-and-tear of the nitrogenous framework probably does occur, but it is small compared to the amount of material required for the energy expenditure during the work.

Fat and carbohydrate may be oxidized. Of these carbohydrate is believed to be the main source of muscular energy. The measurements of the respiratory quotient, already described, are evidence for this. Carbohydrate is the more probable source of energy because of the relation of lactic acid to glucose



Glycogen gives rise to sugar when muscle contracts.

Another source from which lactic acid may be derived is hexose phosphate (Embden). If hexose phosphate is decomposed, phosphoric acid would be set free, and part of the acidity of muscle may be due to phosphoric acid. It must not be forgotten, however, that lactic and phosphoric acids are not necessarily free acids in muscle as they exist probably mainly in the form of salts.

**The Forms of Energy Available for Muscle Contraction.** The association of heat production with muscular activity suggests that the muscle may act as a heat engine. That this is impossible was shown by Fick (1893). The amount of energy liberated as external work is at least one quarter of the total amount of energy as heat. This ratio of work done to the total amount of energy transformed is a measure of the efficiency of a machine. The efficiency of a heat engine is determined by the equation on p. 279. The efficiency of muscle may be as great as one quarter and the temperature of the final state is that of the body,  $273^{\circ} + 37^{\circ} \text{ C.} = 310^{\circ}$  absolute; hence if we substitute in the equation we find

$$\frac{1}{4} = \frac{T_1 - 310^{\circ}}{T_1} \therefore T_1 = 413^{\circ}.$$

From this we see that an efficiency of one quarter requires a temperature of  $140^{\circ} \text{ C.}$  for the higher temperature if the lower temperature is that of the body. Therefore we cannot regard muscle as a heat engine and we must look for some physico-chemical process in a solution for the power required for muscular contraction.

**The Behaviour of Muscle during Contraction.** The structure of muscle shows a division into two kinds of material. One is anisotropic, i.e. it rotates the plane of polarized light. This corresponds to the dim bands. The light bands are isotropic. This observation suggests that the dim bands may be subjected to some form of strain. When a muscle contracts the dim band becomes light, but with polarized light it can be seen that the dim band is still anisotropic and that the light band is absorbed by the dim band. The transfer of contents may be due either to osmosis (Graham, 1854) or surface tension (Fitzgerald, 1878).

If one regards the fibrillæ as consisting of a beaded arrangement, the thicker parts of the fibrillæ corresponding to the dim band, the contraction of the muscle may occur by the swelling of the thickened parts to form spheres. Such swelling might be caused either by a change of osmotic pressure or a change of surface tension, the difference being that in the former case the surface would remain at least as great as it was beforehand, whilst with the latter the surface must decrease in extent.

A drawing to scale (Fig. 136) is given showing what would happen if the contraction occurred by swelling of the anisotropic substance. As the ellipsoids swell they push each other apart so that the total volume of the dim band increases and at the same time it shortens. The spaces between the spherical bodies formed from the anisotropic substance will contain all the sarcoplasm which has not passed into the spheres, hence the dim band disappears and the whole muscle can contract to one third of its original length or less (Roaf).

In the case of a surface tension effect (cf. Bernstein) the spheres would be smaller, hence the extent of contraction would be less. It is doubtful moreover how great a force would be left to do external work as a certain amount of work must be done by the surface tension to deform the anisotropic substance. It must not be forgotten that surface tension effects would probably occur when a change of osmotic pressure took place.

Such a mechanism would account for all the known phenomena of muscle contraction. A weight placed on a resting muscle could stretch it by squeezing liquid from the anisotropic substance into the sarcoplasm. A stimulus applied to such a stretched muscle would produce a greater tension as the constituents in the anisotropic substance are more concentrated by the removal of water, i.e. for the same osmotic pressure produced it would require a greater tension to stretch the muscle to the longer length; hence at the longer length an increase of osmotic pressure will cause a greater pull by the muscle.

Fig. 136 is based on frog's muscle, but a similar effect would be shown in the muscles of other animals. Insect's muscle consists of larger fibres subdivided by minute canals. The subdivision merely increases the surface for osmosis so that swelling would occur more rapidly. The extreme rapidity of insect's muscle may be due to its acting isometrically. If the muscle is prevented from shortening, the tension is established more rapidly. It is perfectly obvious that the more the muscle is allowed to shorten the longer the time required as a larger volume of liquid must be transferred from one part of the muscle to another, and the more rapid the shortening the greater the excess of energy required to move the liquid. Although such a description is necessarily crude it gives

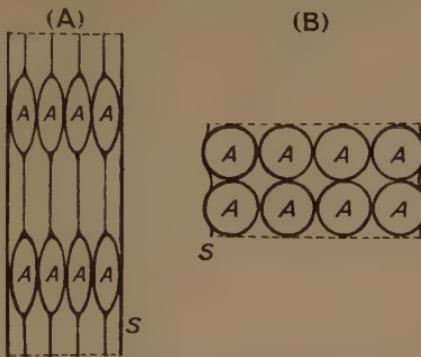


FIG. 136.—Diagram representing Muscle Contraction drawn to Scale.

(A) Relaxed condition, (B) Condition when ellipsoids of revolution swell up to become spherical (modified from Roaf, *Proc. Roy. Soc.*).

some idea of the way in which a muscle might act. The manner in which the osmotic pressure is produced may be by the formation of a protein salt with the lactic and phosphoric acids which are found in fatigued muscles. Such a salt formation would give a negative potential on the surface of muscle because the anion can diffuse whilst the protein cannot (compare p. 161).

The heat changes in muscle follow from general physical considerations. If a muscle is prevented from shortening all the energy must appear as heat. To restore a system to its original condition will require as much energy as that given off in the original process. Further, stretching any elastic structure causes a fall of temperature and allowing it to contract will cause a rise of temperature.

Macdonald (1909) has compared muscular contraction to the release of a spring. The spring is subsequently wound up by the use of some other form of energy in amount equal at least to that set free by the release of the spring.

The processes described in this chapter form a series. Starting with gas exchanges in the lungs which can be satisfactorily explained as a running down of potential of a single form of energy (diffusion), we have examined various activities which include a transformation of energy potential of one sort to a potential of another sort. The final example is one in which a running down of potential chemical energy is used to produce kinetic energy. Living cells seem to avoid the path through heat energy, in that way avoiding a certain amount of loss of energy.

In fact with isolated muscle the efficiency is much greater than one quarter, the figure which was used by Fick in proving that muscle cannot be a heat engine. A. V. Hill has shown that the amount of heat set free during contraction is equal to the external work done. This would mean one hundred per cent. efficiency. As an equal amount of heat is liberated during recovery the efficiency is reduced to 50 per cent. Other processes require an expenditure of energy so that in the intact animal the efficiency is still further reduced.

Part II has dealt with the energy changes in the animal body. It is therefore a branch of the subject of Biological Chemistry. We have been concerned with showing how energy is obtained and expended, and in this description we have had to trace the course of the various chemical substances through the various systems and organs of the body.

We must remember that the mechanical processes described in Part I depend on the energy processes for their production, so that the two must be thought of as complementary parts of a whole.

NOTE.—For further information on the subjects dealt with in Part II, the student should consult H. E. Roaf, *Biological Chemistry* (Methuen & Co.)

## PART III

### REGULATIVE MECHANISMS

The characteristic feature of living organisms is that they exert a directive influence on the processes which occur in them. Thus influences which might produce inharmonious activity of different parts produce a harmonious response, and in this section the processes which unite the various activities of the body will be described.

The individual cells of the body, like unicellular organisms, have local regulative processes, but in multicellular organisms some method is required to correlate one part with another.

There are two ways in which the cells can be regulated, one by the development of a special conducting mechanism, i.e. the nervous system and the other by the circulating fluids, whereby one part can influence other parts by a chemical substance which becomes distributed to all parts of the body.

## CHAPTER XXII

### NERVES AND NERVE STIMULATION : THE NEURON

In Chapter II we pointed out that a muscle can be called into action by direct stimulation or by indirect stimulation through a nerve. We must now study what the nerves are, and the phenomena connected with their stimulation.

A nerve cell or neuron consists of several parts which are shown in Fig. 73. The parts of a neuron are seen to be a cell body containing a nucleus, a long process or axon and short processes or dendrons. The cell body is mainly of importance as a regulator of the nutrition of the rest of the cell. If the processes are cut off from the cell body they die. The long process is the main conducting path and the short processes are paths of communication with neighbouring cells. In certain sensory cells the dendrons are separated from the cell body by a conducting process or axon so that morphologically it is difficult to say which should be called the axon and which the dendron. The cell body consists of protoplasm and a nucleus. In the protoplasm are situated masses of material which stain deeply with aniline dyes: these are called Nissl granules and they atrophy when the cell is fatigued or injured. Certain fibrils run through the cell body connecting the various processes of the cell, but these neurofibrils, like the Nissl granules, may be artifacts produced by the method of preserving the cells.

The dendrons consist of naked protoplasmic processes.

The function of a nerve is best illustrated by the use of a muscle-nerve preparation. If the muscle is observed, or arranged to record its variations in tension, it is found that pinching the nerve causes activity in the muscle. Thus we see that although there is no visible change in the nerve some influence has passed along it to affect the muscle. We can cause the same influence by acting on the nerve in other ways, such as the application of chemicals, heat, or by electrical currents. As mechanical injury, heat and chemicals are not easily controlled and the nerve is liable to permanent injury from them, we most frequently use electrical stimulation to produce nerve activity for experimental purposes. (For methods of electrical stimulation see Appendix.)

We can treat this problem in the same way that we investigated muscle activity, that is, we can study the influence of various physical conditions on the activity of the nerve and in order to show that the nerve has become active we use a muscle as an indicator.

The first point that we have learnt is that a nerve can be stimulated by a variety of physical and chemical processes and that the electrical stimuli are those best adapted for studying the properties of nerves.

#### EFFECT OF VARIOUS EXTERNAL AGENTS ON NERVE CONDUCTION

By stimulating a muscle-nerve preparation at one point and by acting upon the nerve between the point of stimulation and the muscle, it is possible to study the effect of various agents on the propagated disturbance in a nerve.

*Temperature.* The effect of temperature is that the rate of conduction is greater at higher and less at lower temperatures. The usual limits occur, namely, that the conduction stops entirely at low temperatures and that at temperatures above 40° C. the nerve is rapidly killed. The rate of conduction has a temperature coefficient of about 1.78, which suggests an underlying chemical process, but this high coefficient by itself does not justify the conclusion that the nerve impulse is a chemical process.

#### RATE OF CONDUCTION ALONG A NERVE

The rate of conduction can be measured by stimulating a nerve at two different points. If the contractions of the muscle are recorded it is possible to measure the length of time between the application of the stimulus and the response of the muscle. The latent period is longer the further the stimulated point is from the muscle. As all the other conditions are the same the difference in time is due to the time required for the impulse to travel along the nerve. By measurement of the difference in latent period and the distance between the two stimulated points, the rate of conduction can be calculated.

For frog's nerve at room temperature (about 15° C.) the rate is about 28 metres per second. At 37° C. the rate would be approximately that found for human nerves, namely about 120 metres per second.

*Drugs.* Various drugs have the property of stopping the conduction of the nerve impulse, for example chloroform and ether vapour, dilute solutions of alcohol, and gases such as carbon dioxide. If the drug is not too concentrated nor allowed to act for too long

a time the conductivity recovers when the drug is removed. This shows that the nerve is not killed but that its activity is merely suspended ; it is anæsthetized.

*Action of Constant Current.* If a constant current is passed through a nerve by means of non-polarizable electrodes (see p. 39), the nerve undergoes what are termed electrotonic changes. The effect at the two poles is different : thus we find an anelectrotonic condition at the positive pole or anode and a catelectrotonic condition at the negative pole or cathode. This is tested by stimulating the nerve at a neutral region between the two electrodes and reversing the direction of the current so that the pole between the stimulating electrode and the muscle may be either anode or cathode.

Under these conditions the conductivity is decreased at the anode and with strong currents the conductivity of the nerve may be completely stopped ("blocked"). Thus there will be no contraction of the muscle when the anode of the polarizing current is

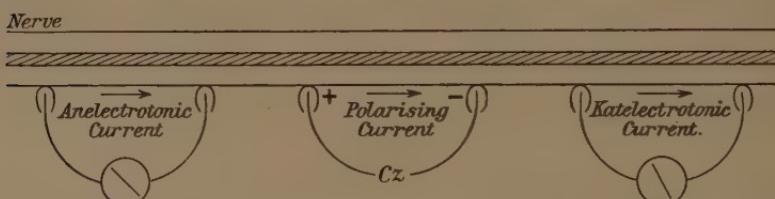


FIG. 137.—Diagram showing Direction of Anelectrotonic and Katelectrotonic Currents (Flack and Hill).

between the stimulating electrodes and the muscle. The reverse occurs at the cathode : thus if any effect is noticed the contraction of the muscle will be greater when the cathode is between the stimulating electrodes and the muscle than when there is no polarizing current.

It must be pointed out that an electrical potential applied to a structure causes a spread of potential (cf. the heart and the electrocardiogram, Fig. 53), therefore differences in potential can be demonstrated in the nerve beyond the non-polarizable electrodes. In Fig. 137 the polarizing current in the centre is represented as causing currents outside the region of the polarizing current.

*Effect of Previous Activity.* The effect of a second stimulus following a previous one after a short interval of time is complicated because there are two factors to consider, namely the effect on the power of conduction by the nerve and the effect on the ease with which an impulse can be started in a nerve. The latter problem will be studied first.

#### Effect of various Agents on the Initiation of a Propagated

**Disturbance in a Nerve.** The application of various reagents to a nerve affect its conductivity as well as its excitability, but we can make use of the ease with which a nerve is stimulated as a test of its excitability. For this purpose we employ electrical stimuli as they can be accurately graded.

*Effect of Intensity of Stimulus on the Response of a Muscle-nerve Preparation.* If a nerve is stimulated by the current from the secondary coil of an induction coil it is found that with a sufficiently weak shock no effect is produced, but if the strength of shock is gradually increased a limit is reached at which a response occurs. This is called the threshold or limen and weaker stimuli are called subliminal. If the strength of shock is still further increased the response of the muscle becomes greater until a maximal effect is produced beyond which no greater response is produced even if the strength of shock is increased. Thus we can speak of the shock which is just at the threshold as minimal and that which produces the greatest effect as maximal ; between these two we have submaximal stimuli. Compare this result with the effect of direct stimulation of muscle by stimuli of different strength (p. 24).

The minimal, submaximal and maximal effects may be due to two causes :

(a) The separate nerve fibres may give varying propagated disturbances ;

or (b) a varying number of nerve fibres may be affected by the different stimuli.

The former is improbable, because, as we shall now show, the propagated disturbance is always the maximum that can be produced in the nerve according to its condition at the moment when the disturbance is travelling along it.

#### EVIDENCE THAT A NERVE IMPULSE IS NOT VARIABLE IN STRENGTH.

In support of the second view the two following results are given :

If a portion of the nerve to a muscle is anæsthetized it is found that if the conduction of the nerve is stopped it is stopped equally for strong or for weak stimuli (Symes and Veley). Caution is required in carrying out this experiment as it does not necessarily follow that all the nerve fibres are anæsthetized at the same instant and a stronger stimulus might cause a propagated disturbance in a nerve fibre which was not anæsthetized. This would appear as if the stronger stimulus had caused a disturbance in the nerve which could pass through a longer length of anæsthetized nerve.

Adrian carried out experiments in which two nerves were treated with alcohol vapour. One nerve had a fairly long piece exposed to the alcohol vapour, the other nerve had the same total length

exposed to the alcohol vapour, but the alcohol was applied to two shorter lengths with a piece of normal nerve fibre between the two anaesthetized portions. The muscle of which the long piece of nerve was treated failed to respond to stimulation, whilst the muscle of which the nerve was treated in two separate sections still responded to stimulation.

As a long piece of nerve exposed to alcohol vapour fails to conduct whilst a short piece will still conduct, it is assumed that the impulse in the nerve is gradually weakened until it is entirely stopped. That the impulse can pass through two short pieces of anaesthetized

nerve suggests that the impulse recovers its intensity on passing through a normal piece of nerve. As the result is the same no matter how short the piece of normal nerve is, the recovery must take place as soon as the impulse reaches a normal piece of nerve.

This deduction is of considerable importance in connection with the variable effect of stimuli of different strengths. In the case of a muscle-nerve preparation we saw that the increased height of contraction corresponding to a stronger stimulus could be explained by the stronger stimulus affecting a larger

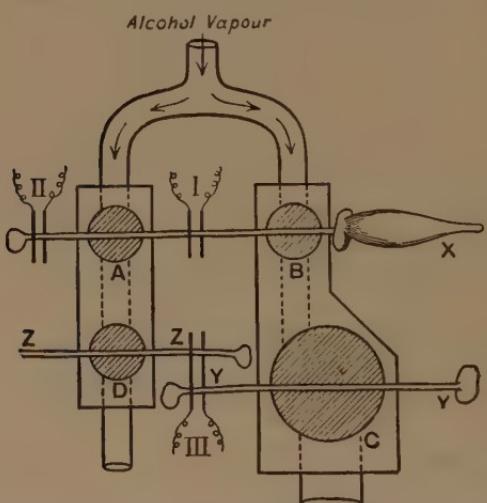
FIG. 138.—Diagram of Apparatus for Anaesthetizing Nerves (Adrian in the *Journal of Physiology*, Cambridge Press).

A and B, two chambers the combined diameters of which equal that of chamber C. When stimulation fails by electrodes III, a response may still be obtained by electrodes II. When the response fails at electrodes II it will also fail at electrodes I. ZZ is a control preparation to show that the electrodes III can still stimulate Z when the response fails in YY.

number of nerve fibres and not by a greater effect on each individual fibre.

The experiments of Keith Lucas on the cutaneus dorsi muscle in the frog show that the heights of the contractions produced by gradually increasing strengths of electrical stimuli increase by a few steps and not by a continuous rise in height as the strength of the stimulus increases.

When a nerve is being stimulated the whole of the current must pass through those nerve fibres which are in direct contact with the electrodes, but in the area midway between the electrodes



the same amount of current is spread over a larger number of nerve fibres, i.e. the current density (current  $\div$  cross section of conductor) is less. Therefore to stimulate these midway fibres a stronger current is required and as the strength becomes sufficient

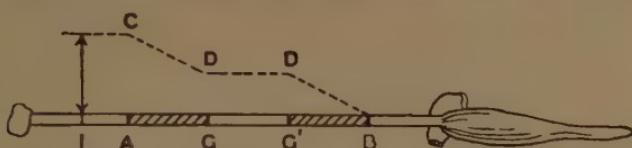


FIG. 139.—To show how a Nerve Impulse would be Extinguished by Two Successive Regions of Decrement if no Recovery took place between the Two Regions (Lucas, *Conduction of the Nervous Impulse*, Longmans, Green & Co.).

AG and G'B = two anæsthetized regions, the total length of which would extinguish the impulse if no normal portion intervened. The distance above AGG'B of the interrupted lines CDD' = diagrammatic representation of the strength of the impulse. On the supposition that no recovery occurs, it is extinguished at B.

to stimulate each additional nerve fibre a greater response occurs in the muscle.

*The Effect of Drugs on the Initiation of a Nerve Disturbance* is complicated by the effects of the same substances on nerve con-

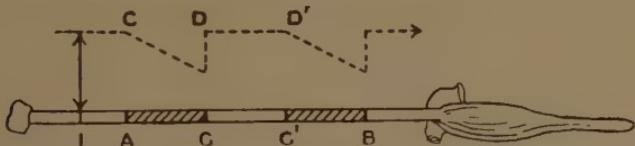


FIG. 140.—To show the Recovery of the Nerve Impulse between Two Regions of Decrement so that the Impulse can pass the Second One and cause Contraction of the Muscle (Lucas, *Conduction of the Nervous Impulse*, Longmans, Green & Co.).

AG and G'B = two anæsthetized regions, the total length of which would extinguish the nerve impulse if no normal portion intervened. The distance above AGG'B of the interrupted line CDD' = diagrammatic representation of the strength of the impulse showing its immediate recovery in the normal portion so that it can pass the second region of decrement.

duction. Thus unless one can find a drug which has no effect on nerve conductivity it is not possible to affect the excitability by drugs as an independent effect.

**Effect of Constant Current on Excitability of Nerve.** This can be tested by stimulating a nerve close to that non-polarizable electrode which is the nearer to the muscle. It is found that the anelectrotonic condition makes the nerve less excitable, so that a stronger stimulus is required to produce a contraction in the muscle, whilst the catelectrotonic condition renders the nerve more easily excitable, causing it to respond to a weaker stimulus. The effect on the excitability thus corresponds to the effect on the conductivity.

*Other Evidences of the Passage of a Propagated Disturbance in*

*Nerve.* The activity of muscle is accompanied by heat production, increased use of oxygen, increased formation of carbon dioxide, use of stored materials, and by electrical changes. Of these changes the only ones that have been shown to occur in nerve are the electrical changes and an increased formation of carbon dioxide.

A. V. Hill has surrounded a nerve by a thermopile capable of showing a rise of  $1 \times 10^{-6}^{\circ}$  C. and he failed to find any evidence of an increase in temperature when the nerve was stimulated.

The nerve is extremely sensitive to lack of oxygen, but up to the present no definite proof has been given that activity of nerve causes an increased use of oxygen. In the absence of oxygen nerve



FIG. 141.—Record showing Effect of Stimulation in Regions of Cathode and Anode (M. S. Pembrey).

Upper curve shows increase in height of contraction when an electrotonic current is passed in, so that a minimal stimulation occurs in the region of the cathode (K ——). Lower curve shows the abolition of response when an electrotonic current is passed in, so that the stimulus occurs in the region of the anode (A ——).

fibres soon lose their conductivity, but we have no proof that the conduction of an impulse requires increased oxygen consumption.

When a nerve is stimulated repeatedly its conductivity is improved, and Waller has shown that small quantities of carbon dioxide improve the conductivity of nerve, from which he deduced that more carbon dioxide was produced by a nerve during activity than when at rest. Tshiro has actually shown that more carbon dioxide is produced by a nerve during activity. This result suggests that more oxygen may be used during nerve activity than when it is at rest.

**Electrical Changes in Nerve Fibres.** The electrical change

which accompanies the passage of an impulse along a nerve is in many respects similar to the electrical change that accompanies a wave of muscle contraction.

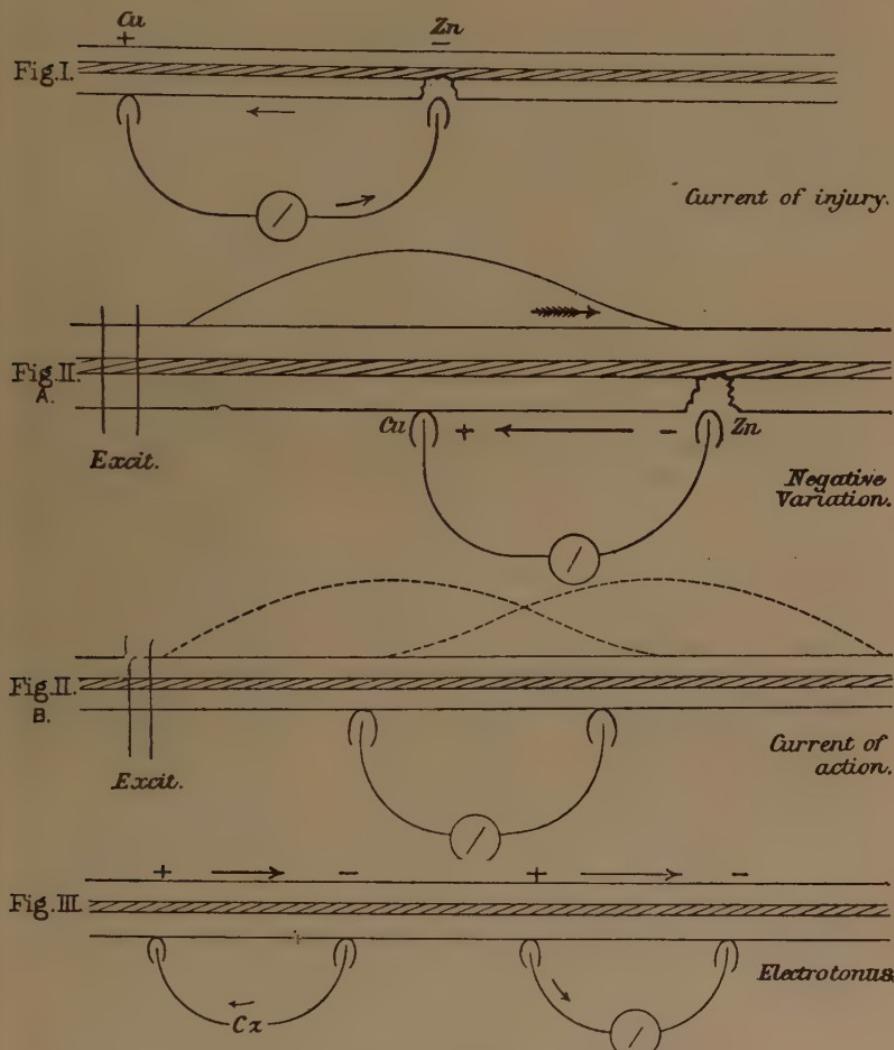


FIG. 142.—Diagrams to Illustrate Electrical Conditions of Nerves (Flack and Hill).

I. Direction of current of injury.

II. Decrease of current of injury due to activity (negative variation).

III. Diphasic current of action. The two waves show the successive condition at the electrodes as the impulse travels from the exciting electrodes towards the right.

III. Shows the direction of current in the galvanometer due to a constant current from the battery ( $Cz$ ) (Electrotonus).

If non-polarizable electrodes are placed on a nerve it is found that injury to the nerve causes that portion of the nerve to act as the negative pole of a battery. If, on the other hand, the nerve is not injured but merely stimulated, it is found that a wave of

negativity passes along the nerve, reaching first the electrode nearer the point stimulated, and later the electrode further away. This produces a diphasic variation in the record of the galvanometer (see Fig. 142).

The constant association of this electrical variation with an effect of the nerve on the muscle or central nervous system as indicator is sufficient warrant for us, when there is no other indicator available, to use the electrical change as evidence that a propagated disturbance has passed along the nerve.

#### Conduction of a Nerve Impulse in both Directions.

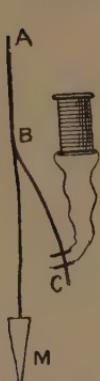


FIG. 143.—  
Paradoxical Contraction of Muscle due to Stimulation of a Branch of its Nerve (from Waller's *Human Physiology*, Longmans, Green & Co.).

If we stimulate a nerve half-way along its length, and above the stimulating electrodes we place a pair of non-polarizable electrodes for recording the electrical changes in the nerve, we find that accompanying the contraction of the muscle there is an electrical change in the nerve. From this we conclude that the propagated disturbance passes both ways from the point of stimulation, i.e. downwards, causing the muscle contraction, and upwards, causing the electrical change.

There are two other experiments which show that an impulse can pass along a nerve in either direction.

*Paradoxical Contraction* (Fig. 143). A muscle-nerve preparation is made in which a branch nerve is found coming off from the nerve to the muscle and

this branch is stimulated at C. The muscle M contracts, showing that an impulse must have passed up CB in order to affect the nerve to the muscle.

*Gracilis Experiment* (Fig. 144). The gracilis muscle is supplied by a nerve which branches just before it reaches the muscle. The muscle is divided at the tendinous intersection which exists near its middle. Excitation limited to one branch of the nerve causes both portions of the muscle to contract. This result is of importance in connection with phenomena, such as the axon reflex, which occur in the nervous system.

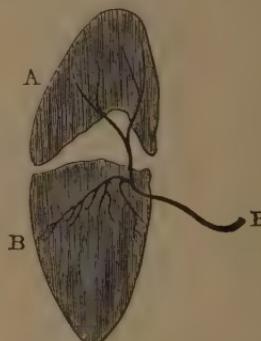


FIG. 144.—Kühne's Gracilis Experiment to show Conduction in Both Directions in an Efferent Nerve.

The muscle is divided at its tendinous intersection into two parts, A and B; excitation localized at the peripheral end of the nerve after it has branched to either A or B causes contraction of both portions of the muscle (Waller, *Human Physiology*, Longmans, Green & Co.).

### Nature of Electrical Stimulation

When a nerve is stimulated by an electrical current we saw that it required a certain minimal potential difference. If we examine this subject more closely we find that there are three factors to be considered.

Firstly there is the strength of the current. This is best expressed in terms of pressure or potential because the high resistance of the tissues makes the amount of current almost proportional to the electro-motive force. It is not possible to measure the amount of current flowing through any individual cross-section of the tissue, but we can measure the electro-motive force supplied to the electrodes. The current is related to the resistance and potential by the formula

$$C = \frac{E}{R}.$$

Secondly there is the duration of the current. This, multiplied by the current, gives the quantity of electricity on  $Q= Ct$ .

The third factor is the rate at which the current changes. Most physical instruments which respond to a unidirectional current do so independently of the rate at which the potential is established, but with living tissues it is found that it is necessary that the potential must be established within a certain time interval : that is, the rate of change of the current is important.

If we plot in a diagram the potential at which a nerve is stimulated against the time that elapses between the commencement of the current and when it reaches its maximum, we shall have a graph showing the rate of increase of the current. It is found that there is a slope to the curve representing a certain rate of increase of the current at which stimulation will just occur. Any rate of increase less than this will fail to stimulate even if the maximum potential is above the minimum necessary to stimulate, and any greater rate of increase will stimulate provided a certain minimum potential is exceeded.

Thus if we wish to study the effects of electrical stimuli in starting a nerve impulse we must have the rate of increase in potential sufficiently rapid. When a current is started suddenly and after a brief interval of time is abruptly stopped, it is found that there is a relationship between the duration of the current and the potential which suffices to produce stimulation.

Fig. 145 shows the relation between duration of current and potential which will stimulate the nerve-free muscle fibre of the toad's sartorius. With potentials less than 0.15 volts no contraction occurs no matter how long the current passes through the muscle, and with durations less than  $3\sigma$  no contraction occurs even if the potential is fairly high. The "excitation time"

(chronaxie) has been defined as the duration of the current which will just cause stimulation when the potential is double the least

potential that will produce stimulation with infinite duration of the current. This is a measure of the quickness of the tissue to respond to electrical stimulation. Very rapid alternations of current, because of their brief duration, have only a heating effect on the body. Thus it is possible to pass through the body enough current to

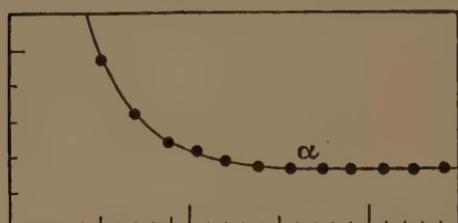


FIG. 145.—Excitation of Muscle-Substance ( $\alpha$ ) in the Extreme Pelvic End of a Toad's Sartorius.

Ordinates, 1 division = 0.1 volt; abscissæ, 1 division = 0.001 sec. Liminal voltage begins to rise at 0.015 sec., and is doubled at 0.007 sec. or  $7\sigma$  (Keith Lucas, with permission of the editor of the *Journal of Physiology*).

light an electric lamp without any effect on muscle or nerve, provided the alternations are above the rate of 10,000 per second.

TABLE XLIII  
EXCITATION TIME (IN SECONDS). (LUCAS.)

|                                 | Frog.   | Toad.   |
|---------------------------------|---------|---------|
| Sartorius Muscle . . . . .      | 0.003   | 0.007   |
| Sciatic Nerve . . . . .         | 0.00035 | 0.00038 |
| " $\beta$ " Substance . . . . . | 0.00025 | 0.0001  |

Stimulation of a nerve trunk gives a different curve from that obtained with muscle fibres. Fig. 146 shows the effect of stimulating the middle of a toad's sartorius. The lower curve,  $\alpha$ , is much the same as that in Fig. 145 and it may be ascribed to the stimulation of muscle fibres. When the duration of the current is too short to stimulate the muscle fibres and the potential is increased a portion of a second curve,  $\gamma$ , is seen. This curve seems to correspond to the curve given when a nerve trunk is stimulated. The nerve is more easily stimulated by currents of short duration than is muscle, but it requires a higher potential, which is equivalent to saying that a muscle is more easily stimulated by a low potential, but it requires the current to pass through it for a longer time. A third curve,  $\beta$ , is seen in Fig. 146, with high potential and short duration of the current. This third curve persists after the muscle has been curarized. As curare interferes with the passage of an impulse from nerve to muscle this third curve cannot be due to anything in the nerve fibres. If this third curve really depend upon a third substance present in muscle, it may be due to the presence of a junctional substance between muscle and nerve.

Thus stimulation of a muscle containing nerve fibres indicates

that there may be three excitable substances present. The first two are obviously the muscle fibres and the nerve fibres. The third, if it is really present, may be the junction between the nerve and muscle which can be shown histologically as the motor end plate.

Turning to the possible physio-chemical basis of the excitability of a tissue by electrical stimulation, the relation between current strength and duration is suggestive of a concentration of ions by electrolysis. The movement of ions by an electric current requires a certain amount of time and the concentration reached depends on the strength of current multiplied by the time during which it is flowing. When a concentration of ions has been produced they will diffuse away and the concentration maintained will be a balance between the effect of the current and the rate of diffusion.

That the current must increase at a definite rate is suggestive of some effect similar to an inductance. During the increase of current in a coil the self-induction resists the increase so that the potential between the two ends of the coil is greater than that due to the ohmic resistance of the coil. When a steady current is flowing the potential between the two ends of the coil is much less, being only that due to its ohmic resistance. A strong steady current has no effect on an inductance, but the rate of change of current does affect it, hence the analogy between an inductance and the stimulation of tissues in which rate of change of current is so important.

**Refractory Period of Nerve.** If a nerve is stimulated by two stimuli at different time intervals apart it can be shown that there is a period during which the nerve is inexcitable or excited with greater difficulty. The method consists in recording the nerve impulse by the electrical change in the nerve. If for frog's nerve

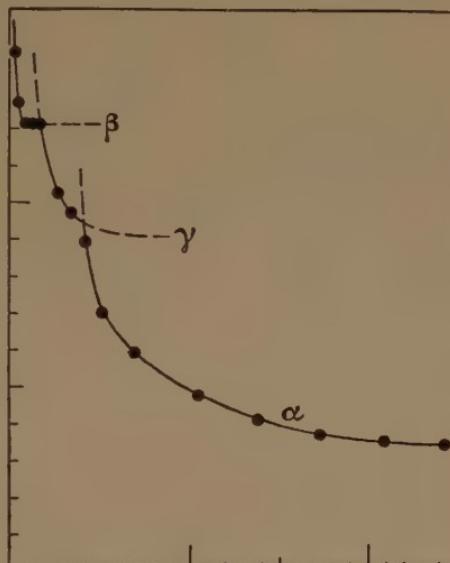


FIG. 146.—A Complex Curve obtained by Excitation in the Middle of the Toad's Sartorius.

The curve consists of three parts, the lowest being due to excitation of the muscle fibre  $\alpha$  (compare with Fig. 145); the middle,  $\gamma$ , corresponding to that for nerve fibres; the third,  $\beta$ , may be ascribed to neuromuscular junction. Ordinates, 1 division = 0.1 volt; abscissæ, 1 division = 0.001 sec. or 1  $\sigma$  (Keith Lucas, with the permission of the Editor of the *Journal of Physiology*).

the interval between two stimuli is less than 0.007 sec. ( $7\sigma$ ) at 4° C. and less than 0.003 sec. ( $3\sigma$ ) at 12°, the second stimulus is ineffective.

**Non-fatiguability of Nerve.** If a muscle or muscle-nerve preparation is stimulated it becomes fatigued. By the following procedures it can be shown that nerve does not become fatigued. Two muscle-nerve preparations are arranged so that they can be stimulated by the same current. One nerve has a constant current passed through it so that the impulse is blocked by the anelectrotonic condition at the anode. After the muscle of the preparation, the nerve of which is not subjected to the constant current, is fatigued, the constant current is stopped. The muscle which has been protected by the constant current now contracts normally. This shows that the nerve is not fatigued but that the fatigue of the stimulated nerve must be due to the nerve ending or the muscle fibre.

If the muscle which has ceased to respond to stimulation through its nerve is stimulated directly, it will respond, showing that the muscle has not been completely fatigued. The fatigue is largely at the junction between nerve and muscle.

The refractory period of the nerve may be considered to be a type of fatigue of short duration. In other words activity must be followed by a period of rest before another impulse can be made to travel along the nerve.

**Relation of the Body of the Nerve-cell to its Processes.** If a nerve fibre is separated from its cell body the nerve can still carry impulses to its attached structures, as is shown by the stimulation of the nerve of a muscle-nerve preparation, but if a nerve in an animal is cut it is found that in a few days the portion separated from the cell body no longer transmits an impulse when it is stimulated.

When examined microscopically changes can be seen in the nerve fibres. Before we can discuss these it is necessary to study the structure of the normal nerve fibres.

There are two kinds of nerve fibres, myelinated and non-myelinated, in which the difference consists in the presence or absence of a fatty sheath.

A myelinated nerve fibre consists of a central core or axis cylinder; this forms the process which is a continuation of the protoplasm of the cell body. Surrounding the axis cylinder is a tube of fatty material called the myelin sheath. It is interrupted at intervals, the interruptions being called the nodes of Renvier. It is this sheath which causes the cross section of a nerve fibre to appear as an annular structure.

Covering the myelin sheath is a thin membrane known as the primitive sheath or neurilemma. Associated with the neurilemma

are occasional nuclei, usually one to each section between two nodes (internode). At nodes themselves the axis cylinder is covered merely by the neurilemma.

A non-myelinated nerve has merely an axis cylinder with the neurilemma and its nuclei.

**Wallerian Degeneration.** When a nerve is cut the most obvious changes are in the myelin sheath. In three to four days this sheath is seen to lose its smooth appearance and to break up into globules ; at the same time a change takes place in its staining reactions. The sheath of a normal nerve fibre stains black with 1 per cent. osmic acid, suggesting the presence of an unsaturated fatty material, but if treated with a mixture of Muller's fluid two parts and 1 per cent. osmic acid one part (Marchi's fluid), the osmic acid does not stain the myelin sheath. During degeneration the fatty globules stain black by Marchi's fluid, and this is used as a test for degenerating nerves. Accompanying the breaking up of the myelin sheath the axis cylinder also breaks up into fragments. After three to four weeks the fatty material of the myelin sheath is absorbed, so that the fibre no longer stains with either 1 per cent. osmic acid or Marchi's fluid. The absorption of the fat may be due to leucocytes or to the cells of the primitive sheath. The latter increase in number so that at the later stages of degeneration the nerve fibre is represented by a row of nucleated cells (band fibre).

The further fate of the nerve fibre depends upon whether it is reconnected or not with a cell body. If not reconnected the cells of the primitive sheath disappear and the nerve fibre is replaced by connective tissue, but if the nerve is reconnected, a new axis cylinder may grow down the sheath. As the axis cylinder grows down the sheath a new coat of myelin is formed and the nuclei decrease in number until each internode is represented by a single nucleus as before.

The end of the axon connected to the nerve cell may degenerate for the length of one node, but it soon commences to grow, and if it does not reach a sheath into which it can grow it may form a coiled or bulbous extremity. The cell body shows changes such as the disappearance of its Nissl granules, vacuolation and excentricity of its nucleus, and if the axis cylinder does not grow into a sheath



FIG. 147.—Wallerian Degeneration in a Cat. Stained by Marchi's Method ( $\times 600$ ) (from Mott in Allbutt's *System of Medicine*).

the cell body may atrophy from disuse. The changes in the cell body are known as chromatolysis.

**Effect of Constant Current on Nerve.** In previous paragraphs we saw that a constant current applied to a nerve causes an increase in excitability and conductivity at the cathode and a decrease in both at the anode.

If we arrange a muscle nerve preparation so that a constant current can be sent through the nerve it is possible to send the current in either direction, i.e. from near the muscle towards the cut end of the nerve (ascending current) or from near the cut end towards the muscle (descending current). In the former case the anode is near the muscle and the cathode further away, and in the latter case the positions of the poles are reversed. Under these conditions a definite order of events will result.

The stimulation is most easy to produce at the cathode on starting the current, therefore with the weakest current a contraction will occur at the closing of the key, no matter in which direction the current is passing. By increasing the current it is possible to obtain contraction as the result of stimulation at either make or break of the current.

With higher potentials the effect of the constant current on nerve conductivity interferes so that unless the stimulation occurs at the electrode nearest the muscle no contraction will result, i.e. there will be no stimulation at make when the current is ascending nor at break when the current is descending.

If we call these potentials weak, medium and strong respectively, we can express the results in a table.

TABLE XLIV

## STIMULATION OF NERVE BY THE CONSTANT CURRENT (PFLÜGER)

| Relative Potential Differences. | Direction of Current. |        |                      |        |
|---------------------------------|-----------------------|--------|----------------------|--------|
|                                 | Ascending.<br>Make.   | Break. | Descending.<br>Make. | Break. |
| Weak . . . . .                  | C                     | O      | C                    | O      |
| Medium . . . . .                | C                     | C      | C                    | C      |
| Strong . . . . .                | O                     | C      | C                    | O      |

If the intermediate potential is too weak or too strong the medium potentials may cause small and large contractions instead of two equal contractions, and sometimes a tetanus may occur at break of the strong ascending current (Ritter's tetanus).

*Stimulation occurs at the Cathode when a Current is started and at the Anode when it is stopped.* We can show in a muscle that stimulation occurs at the cathode at start of the current and at the anode when the contact is broken. Usually when a nerve is stimulated the current going through it causes physiological cathodes

as the current flows in at one side of the fibre and out at the other side.

The experiment can be carried out using a curarized sartorius. The muscle is held by a slight pressure about one-quarter of its length from the end attached to the writing lever. Arrange two non-polarizable electrodes on the portion of muscle between the clamp and the fixed end of the muscle. Now on stimulating the muscle no record will be shown until the muscle wave has passed beyond the clamp to the free end of the muscle. On stimulating the muscle with make and break shocks it will be found that a stronger current is required to cause a contraction at the break than with the make. Further the latent period is longer at make of the current when the anode is near the clamp and the reverse at break of the current.

The interpretation is that the stimulation occurs at the cathode at make of the current and at the anode at break. Break of the current is therefore equivalent to a weaker current in the opposite direction as the potential must be increased to give any response at break. The pole at which stimulation occurs is shown by the latent period of the contraction as it takes a longer time for the muscle wave to pass from the more distant electrode to the clamp.

If the experiment is carried out on the intact body it is possible to separate the polar effects. By placing a small electrode over a muscle and a larger one on some other part stimulation will occur more easily under the small electrode, because the current density will be greater there than under the large one. It will be found that contraction will occur most easily when the small electrode is cathode at the make of the current (C.C.C. = cathode closing contraction) and least easily when the small electrode is anode at the make of the current (A.C.C. = anode closing contraction). The response at break with either anode or cathode over the muscle requires an intermediate strength of current.

The conditions which determine the sensitivity to stimulation depend partly on the area of the electrodes, but usually the anode closing contraction (A.C.C.) requires a lower potential than the anode opening contraction (A.O.C.).

**Reaction of Degeneration.** After a nerve has been cut the muscles supplied by it undergo a change. This change is shown clinically by the reaction of degeneration.

One change is that the muscle is less responsive to currents of short duration. As shown above this is due to the difference in excitation time between muscle and nerve. Further the contraction of the muscle, when it is elicited, is slow and the duration of the contraction is prolonged.

The A.C.C. may often be more easily produced than the

C.C.C., but this alteration is not an essential condition for the reaction of degeneration.

The reaction of degeneration is important in that it indicates a lesion of the nerve supplying the affected muscles. This motor neuron is often spoken of as the lower motor neuron in contradistinction to the upper motor neuron, which is in the central nervous system.

The conducting properties of nerves are due to prolongations of the protoplasm of nerve cells. These have the property of conducting an influence from one part to another and they can be made active by various forms of external agents, of which the most convenient are electrical currents.

Stimulation by electrical currents suggests that the underlying process requires a definite time interval, which varies for different tissues, but that the strength of current needed to stimulate is inversely proportional to the minimum duration necessary to stimulate them. The current must be produced in the tissue with a certain minimum rate of increase.

When a nerve fibre is separated from its cell body it undergoes Wallerian degeneration, and it may be regenerated if a cell body sends out a new process into the degenerated sheath.

NOTE.—For further reference the student should consult Keith Lucas, *The Conduction of the Nervous Impulse*, Longmans, Green & Co.

## CHAPTER XXIII

### REFLEX ACTION

In studying the properties of muscle and of nerve we have dealt with stimuli applied directly to the muscle or to the nerve. The stimuli produce impulses which travel in either direction from the point of stimulation. This, however, is not the normal manner of stimulation, which is for an impulse to start at one end of a cell and to travel to the other end. In many nerve conductions the result is a reflex action. This is the response of some organ to the stimulation of some peripheral nerve ending. We have already described examples of this action when we pointed out, for instance, that the sight of food causes a flow of saliva.

The structures involved in such a response consist of the following:

1. Some means of receiving the stimulation and for converting it into a nerve impulse, a receptor.
2. A conducting path leading to the nervous system, an afferent neuron.
3. Nervous system itself.
4. A conducting path leading from the nervous system to the organ which responds, an efferent neuron.
5. A structure to carry out the required action, an effector.

Effectors have been studied in connection with the action of muscles and glands. The receptors, afferent and efferent paths, and the nervous system will be discussed in later chapters. In this chapter we shall study the reflex mechanism as a whole by describing the salient features of reflex activities and by illustrating some of the points by a few selected examples.

Granted that the external stimulus must be by some means converted into a nerve impulse we must now prove that there are conducting paths to and from the nervous system. This seems very obvious because cutting a nerve to a muscle paralyses the muscle, but it is possible to show that the two paths are separate ones. The indicator for the nerve impulse of an efferent nerve is the activity of a muscle or a gland, but the indicator for a nerve impulse in an afferent nerve is a sensation or a reflex action. In animal experiments sensations are excluded by anaesthesia or by

removal of the cerebrum, so we must rely on reflexes for the evidence of an afferent nerve impulse.

If we trace a spinal nerve towards the spinal cord we see that it divides into two portions, one entering the ventral surface of the cord (ventral root) and the other entering the dorsal surface (dorsal root). The latter has a swelling on it containing nerve cells (dorsal root ganglion).

It is found that cutting either the ventral or dorsal roots of an area which is giving a reflex response causes the reflex to be abolished. This demonstrates that both ventral and dorsal roots are necessary for a reflex. It must be pointed out that the peripheral distribution of nerve fibres is such that there is a certain amount of overlap, thus destruction of one nerve root does not cause complete absence of either afferent impulses or effector discharges from the area supplied by that nerve.

This is demonstrated by the following experiment on a frog. After the brain has been destroyed the hind legs are tested for reflex movements. Next the urostyle is removed and the lumbar nerve trunks are exposed. Now cut two of the nerves on each side. The nerves cut must be non-corresponding ones, and it is advisable to leave one of the larger on each side so that as many conducting paths as possible are left. Now on testing the two limbs for reflex movements it will be found that although the responses are not so good there are practically no parts entirely denervated. On cutting the remaining nerve on one side and on stimulating it it will be found that practically all the muscles contract. This shows that non-corresponding nerves overlap in their peripheral distribution.

**Bell-Majendie Law.** The function of the two separate roots can be shown by cutting the roots and by stimulating them.

On cutting the ventral roots of spinal nerves, paralysis of the muscles supplied by them results. If the peripheral end of a cut root is stimulated contractions of muscles result, but if the central end is stimulated no result is observed. Therefore this root contains efferent fibres only and there is no evidence of afferent fibres in it. Further, if an animal with cut ventral roots is kept alive it is found that Wallerian degeneration occurs away from the spinal cord, not towards it (B, Fig. 148). This proves that the nerve cells from which arise the axis cylinders forming the ventral root are situated in the spinal cord or other part of the central nervous system.

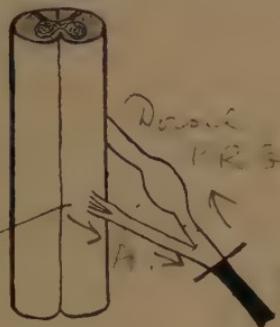
If dorsal roots are cut, reflexes are abolished and the muscles corresponding to that area are relaxed or flaccid. If the peripheral portion of the root is stimulated no muscular contraction occurs and the only result may be a dilation of blood-vessels. This antidromic conduction is a special feature which must be discussed

*Posterior column cells.*

*Posterior column that it is away from*

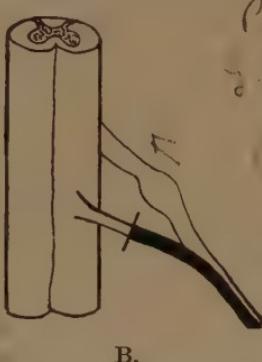
later, and apart from it there is no effect produced by stimulating the peripheral end of a dorsal root.

If, however, the central end is stimulated, movements are produced, thus showing that afferent impulses pass in by the dorsal root. If degeneration is allowed to occur it is found that the direction of the degeneration depends on which side of the dorsal



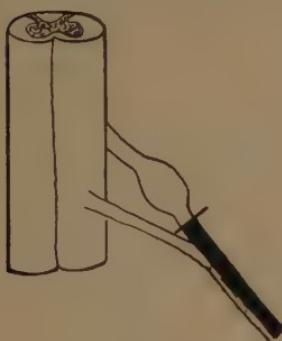
A.

Degeneration of efferent and afferent fibres peripherally to a section of the entire nerve.



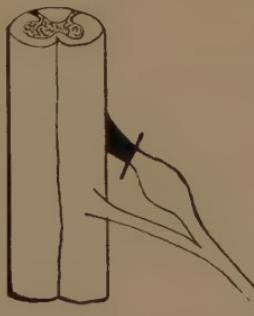
B.

Degeneration of efferent fibres peripherally to a section of the ventral root.



C.

Degeneration of afferent fibres peripherally to a section of the dorsal root external to the ganglion.



D.

Degeneration of afferent fibres centrally to a section of the dorsal root internal to the ganglion.

FIG. 148.—Diagrams to illustrate Wallerian Degeneration of Nerve-roots (Waller, *Human Physiology*, Longmans, Green & Co.).

root ganglion the root is cut. If the cut is peripheral to the ganglion the peripheral end of the nerve degenerates, C, Fig. 148, but if the cut is central to the ganglion the degeneration is into the spinal cord, D, Fig. 148. Degeneration is always away from the ganglion, thus showing that the nerve cells for the afferent fibres are in the dorsal root ganglion.

Examination of the cells of the dorsal root ganglion show that they are peculiar in that they have only a single process coming

off from them. They are oval cells with a single process, but almost immediately the process divides by a T-shaped division, one process running towards the periphery and the other towards the spinal cord. They have potentially two processes, but they come off from the cell as one. It may be that a nerve impulse travels straight from one process to the other without passing down the stalk and back again, and that the cell is merely nutritive and is not necessary for the conduction of the impulse (Bethe).

Thus the ventral and dorsal roots differ in that the former conducts centrifugal or efferent impulses and its nerve cells are in the central nervous system, whilst the latter conducts centripetal or afferent impulses, and its nerve cells are outside the central nervous system in the ganglion of the dorsal root.

**Reflex Arc.** A man is placed in the sitting position with one knee crossed over the other so that the leg hangs down free to move and with a certain amount of tension of the extensors of the knee. The tendon running from the patella to the tibia is given a sharp tap with the side of the hand or some suitable instrument. The leg is jerked forwards by a sudden contraction of the extensor muscle.

This movement might be due to a mechanical stimulation of the muscle fibres by sudden stretching of them when the tendon is jarred. In conformity with this view it may be pointed out that the contraction consists of a single muscle twitch. On the other hand, it has been found that if the reflex arc is interfered with by cutting either the afferent or efferent nerve, or by destruction of the spinal cord, the *knee jerk* can no longer be obtained. There remains the possibility that the reflex arc maintains the muscle in a suitable state to respond to the mechanical stimulus.

As a knee jerk can be obtained in animals it has been studied by experimental methods. An examination of the objections raised to the knee jerk being a reflex illustrates the way in which such a problem may be studied.

1. The objection that the knee jerk is a simple twitch and not a tetanic contraction is not of importance, because it can be shown that other simple twitches are reflex responses. The extensor thrust obtained by greater pressure on the pad of the hind foot of a cat or dog is a single twitch. Here there is no possibility of a direct stimulation of the contracting muscle such as might occur when the patellar tendon is tapped.

Reflex winking of the eyelid is a single twitch. Here again there is no possibility of direct mechanical stimulation, as the cause of the movement is generally visual.

2. The second objection is that the response to the stimulus is so rapid that there is not time enough for an impulse to travel to the spinal cord and back again.

Measurements by Jolly, however, show that there is time for the various processes to occur, hence an impulse may travel to the central nervous system and back again. His experimental procedure was to record the electrical change in the muscle and nerves. The mechanical stimulation was recorded by the striking hammer making an electrical contact when it touched the skin surface.

The following table gives the time intervals measured in sigmas ( $\sigma = 0.001''$ ) for the knee jerk as recorded by Jolly.

TABLE XLV

The time intervals measured were—

|   |                   |
|---|-------------------|
| The time between striking the tendon and the appearance of the electrical change in the extensor muscle . . . . .               | $5.5\sigma$       |
| The time between striking the tendon and the appearance of an electrical change in the afferent nerve . . . . .                 | $0.5\sigma$       |
| The time interval between stimulation of the efferent nerve and the appearance of the electrical change in the muscle . . . . . | $1.5$             |
| Calculated time for nerve impulse to travel 17 cm. at 120 metres per second . . . . .   | $1.4$             |
| Time left over for passage of the impulse through the spinal cord . . . . .   | $2.1$             |
|   | <hr/> $5.5\sigma$ |
|   | $5.5\sigma$       |

Further evidence for the reflex nature of the knee jerk is the fact that the flexor muscles relax when the extensors contract. The significance of the last point will be seen after the student has studied the regulation of reflexes.

The clinical importance of the study of such reflexes as the knee jerk is that any interruption of the reflex path causes loss of the reflex. Thus it is possible to find out where a lesion has occurred. The reflexes may be studied at each joint and from the anatomical data one can find out what nerves, nerve roots, or what part of the spinal cord is affected.

An important function of the cephalic portions of the nervous system is to control reflexes, hence an injury high up may cause exaggerated reflexes. Thus a knee jerk which is too easily produced or excessive in degree may indicate a lesion of what is called the upper motor neuron.

**Synapse.** Whenever one nerve cell comes in contact with another the processes are interlaced. It is not thought that there is direct continuity of structure. This contact is known as a synapse. The time interval left over in the experiment on the knee jerk is called the synaptic loss or reduced reflex time.

It has been shown that a reflex which has to cross from one side of the body to the other takes longer than a reflex that does not need to cross. This greater time interval is ascribed to the fact

that there are more synapses to be passed through in the former than in the latter case.

### Characteristics of Reflexes

Owing to the presence of synapses in the path of a reflex one finds that the result of stimulating a reflex arc differs from the effect of stimulation of a motor nerve. The characteristic features of conduction in the reflex arc are (Sherrington) :

1. A longer time interval between application of the stimulus and the response than is required for the individual processes of nerve conduction, etc., as tabulated on p. 319 (see Fig. 149).  
2. Prolongation of the response beyond the period of the application of the stimulus (after discharge) (see Fig. 150).  
3. The rhythm of the response may differ from the rhythm of the stimulus (see Fig. 151).  
4. Less close correspondence between the grading of the intensity of the stimulus and the magnitude of the response.  
5. A succession of stimuli is generally more effective than a single stimulus (temporal summation).  
6. Conduction through the reflex arc is unidirectional, not bi-directional as in a nerve trunk.  
7. Ease of fatigue.  
8. Great variability of threshold to stimuli.  
9. More marked refractory period, facilitation, inhibition (see Fig. 152) and shock than in nerve trunks.  
10. Great susceptibility to lack of oxygen.  
11. Great susceptibility to drugs, e.g. anaesthetics.

These features are believed to depend on the presence of synapses in the reflex arc.

#### 1. Latency of Reflex Action or Synaptic Loss.

The latency of a process is the sum of all the various stages which preceded the visible result. The various factors concerned are summarized in Table XLV, showing the measurements of the time intervals in the knee jerk. The latency due to the synapses is the portion left after subtracting all the other intervals from the time intervening between the application of the stimulus and the commencement of the response.

The more complicated the path through which the impulses must pass the longer the latency.

Fig. 149 shows the difference in the latent period when a muscle is caused to contract by stimulation of its motor nerve and reflexly.

## 2. Prolongation of Response or After-discharge.

When a muscle-nerve preparation has been stimulated the response stops as soon as the stimulation ceases. If fatigue has occurred the muscle may take some time to relax to its original length.

In the case of reflexes active contraction may continue for some time after the stimulation has ceased.

Fig. 150 shows how after-discharge increases with the strength of the stimulus, although its duration is the same in each case.

## 3. Rhythm of the Response.

The rhythm at which a process occurs is not dependent on the rhythm of the stimulation. Such a movement as the scratch

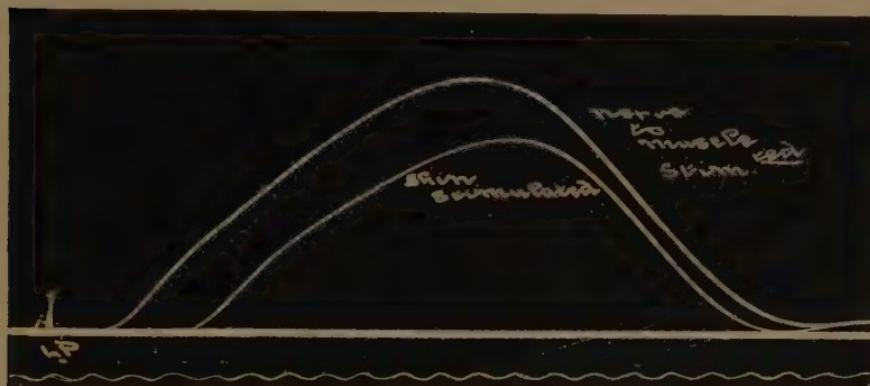


FIG. 149.—Latent Periods for Responses of Muscle to Stimulation of the Motor Nerve and Stimulation of Skin in a Frog.

The difference shows the latent period due to the reflex arc. Time marking in 1/100 secs.  
(Tracing kindly lent by Dr. W. A. M. Smart.)

reflex depends mainly on the dimensions of the moving parts. A moving system requires least energy expenditure when its rhythm corresponds to its rate of vibration as a pendulum. This means that the length and weight of the moving parts must be considered. The scratch reflex, in the dog, consists of a rhythmical to-and-fro movement of the hind leg directed towards a saddle-shaped area on its back. Fig. 151 shows that the frequency of movement is almost the same whether the reflex is brought about by mechanical stimulation or electrical stimuli, and the frequency does not correspond with that of the induction shocks.

The rhythm is slower in large dogs than in small, probably because of the size of the moving parts. It is true that the rhythm may vary in the same animal, but that depends more on the strength of the stimulus than on its frequency. Accelerated or retarded rates involve more muscular interference with the rhythm.

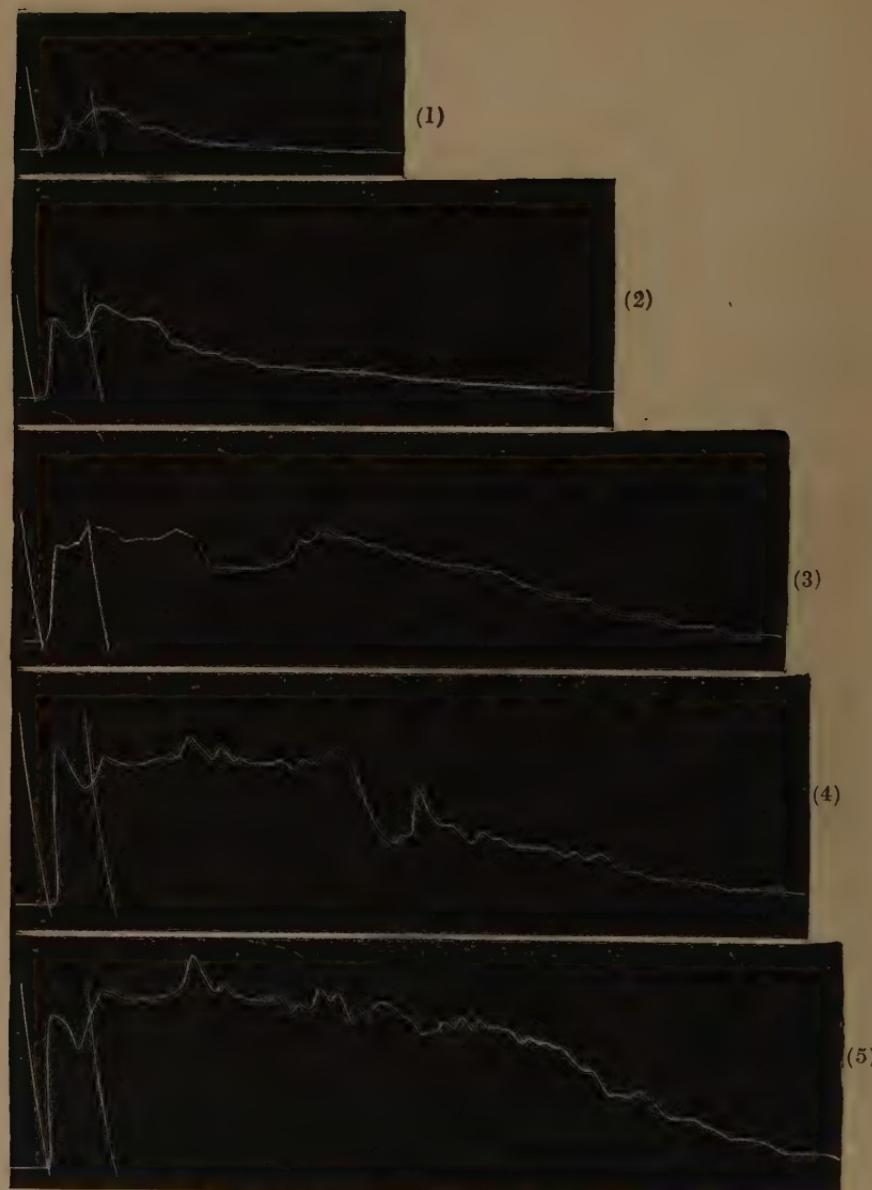


FIG. 150.—Flexion Reflex with After-discharge (Sherrington, *Integrative Action of the Nervous System*, Yale University Press).

Elicited by 10 break shocks at the rate of 20 per second, i.e. stimulation lasting 0.5". Intensity of stimuli increased by bringing secondary coil towards primary and measured in Kronecker units. The amount of reflex is measured by the area between the myograph curve and the base line.

|                    | Stimulus. | Whole<br>Reflex. | After-<br>discharge. | Response<br>during<br>Stim. | % of whole<br>formed by<br>After-discharge. |
|--------------------|-----------|------------------|----------------------|-----------------------------|---|
| First reflex . . . | 30        | 12               | 9                    | 3                           | 75  |
| Second " . . .     | 45        | 52               | 43                   | 9                           | 81  |
| Third " . . .      | 65        | 130              | 118                  | 12                          | 91  |
| Fourth " . . .     | 85        | 176              | 158                  | 18                          | 90  |
| Fifth " . . .      | 100       | 258              | 236                  | 22                          | 91  |

**4. Lack of Correspondence between Intensity of Stimulus and Magnitude of Response.**

The magnitude of a reflex response depends upon so many factors that it is not possible to find any definite relationship between the



FIG. 151.—Tracing of Flexion of the Hip in the "Scratch-reflex" of a "Spinal-dog" (Sherrington, *Integrative Action of the Nervous System*, Yale University Press).

In A the reflex was evoked by lightly rubbing the skin at a point behind the shoulder, in B and C by unipolar faradization with weak double-induction shocks applied to the same point of skin through a needle lightly inserted among the nerve roots. Time marking in seconds. Lower signal marks the time of application of the stimulation. At top of B and C the frequency of the double-induction shocks is shown. Note that the frequency of the rhythmical movements is the same in all three.

stimulus and the response. Within limits a stronger stimulus will produce a stronger response, but the relationship is not so direct as in the stimulation of a motor nerve.

**5. Ease of Stimulation by a Succession of Stimuli.**

A single stimulus may fail to excite a reflex response, whilst a succession of weaker stimuli may be effective. A single strong stimulus may produce an effect, but such effect may be due to the fact that electrolysis or some other result of the stimulus may have caused a series of impulses to pass up the afferent nerve.

**6. Unidirectional Conduction.**

It is not possible to produce any effect through the spinal cord by stimulation of an efferent nerve. We have shown previously that an impulse will pass along a nerve in either direction, hence the unidirectional conduction in a reflex is due to some other factor than the nerve fibre.

**7. Ease of Fatigue.**

Reflexes can be fatigued, whereas we saw that a nerve fibre does not become fatigued. The fatigue is not entirely due to muscle fatigue because after a muscle has ceased to respond to nerve stimulation it will respond to direct stimulation. Similarly the fatigue of a reflex can be shown to be due to something which is neither muscle nor nerve.

**8. Variability of Threshold.**

The same strength of stimulus does not reproduce the same response with the same degree of regularity that would be obtained in a muscle-nerve preparation.

**9. Inhibition, Facilitation, Shock.**

Inhibition is a process whereby a reflex response is interrupted, although the stimulus which produced the reflex still continues : this is shown in Fig. 152.

Facilitation is a process whereby concurrent stimulation of two afferent paths unites to produce an effect. Either stimulus by itself may be ineffective, or if effective the response to both is greater than the response to either stimulus singly.

Not only concurrent stimuli with similar end effects, but successive stimuli also have a facilitating effect. "A parasite travelling across the receptive field of the scratch reflex" would provide such a successive series of stimuli. "In such a sequence the threshold of each succeeding reflex is lowered by the excitation just preceding its own" (Sherrington).

**Spinal Shock.** After cutting the spinal cord a condition results in which reflex response is absent or extremely difficult to produce. The severity of this shock is directly proportional to the grade of

development of the nervous system. In such animals as the frog it is very slight compared to the effect in a monkey.

#### 10. Susceptibility to Lack of Oxygen.

Although a muscle-nerve preparation will respond after being kept in an atmosphere of nitrogen the responses of the spinal cord will fail if the circulation has been stopped for two or three minutes. This effect of the lack of oxygen is shown by the rapid failure of reflex responses in an experimental animal when the circulation fails.

#### 11. Susceptibility to Drugs.

The action of drugs is especially marked on the synapses. For instance a nerve may be rendered incapable of conducting an impulse by the action of such drugs as chloroform, ether or alcohol, but the concentrations of these substances required to produce this effect is much greater than the concentrations which abolish reflex action. General anaesthesia is produced by this interference with conduction across synapses.

**Fatality of Responses.** In an experimental study of reflexes it is very striking how the response follows the stimulation. They are apparently adapted to a purpose such as the removal of an irritating object in the case of the scratch reflex. It is by the intervention of inhibition that reflexes are controlled.

**Prepotency.** When two stimuli are applied which would produce antagonistic effects we see the benefit of inhibition. A reflex occupies the whole nervous system of an animal. When a dog scratches it must balance itself on three legs; this requires a compensatory curve of the spinal column: in fact the whole attitude is adapted for scratching. Now suppose that during the process of scratching the animal receives a stimulus which would make it run away. Both responses cannot occur at once because the same sets of muscles are needed for both actions. The muscles are supplied by nerves

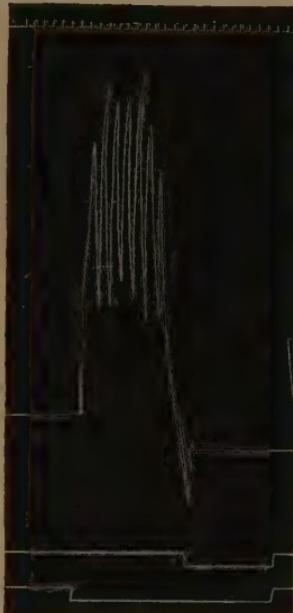


FIG. 152.—Scratch Reflex cut short by Excitation of the Skin of a Digit of Opposite Hind Foot (from Sherrington's *Integrative Action of the Nervous System*, by permission of Yale University Press and Messrs. Constable & Co., Ltd.).

Lower signal marks application of stimulus which excites the scratch reflex. Upper signal shows time of application of stimulus to opposite hind foot. Time marking in  $\frac{1}{2}$  secs.

which form the *final common path* and this path can be occupied by only one reflex pattern at a time.

The impulse which does gain command of the final common path is called the prepotent impulse. Prepotency is not determined entirely by the strength of the stimulus because, other things being equal, a harmful stimulus, such as that produced by firmly squeezing a dog's paw, has precedence over a purely luxurious reflex, such as scratching. The dog withdraws its paw from the noxious stimulus and the scratching is arrested (see Fig. 152).

**Irradiation.** When one hind leg of a spinal frog is held whilst acid is applied to that flank the other leg attempts to wipe away the acid. The spreading of a reflex to other paths is known as irradiation. The convulsions that occur during asphyxia may be the result of the spread of reflex respiratory movements to all the muscles of the body.

**Reversal.** Some substances such as tetanus-toxin and strychnine cause a reversal so that what should be an inhibitory is converted into an excitatory process.

When strychnine is injected the slightest stimulus, such as blowing on the skin of a spinal frog, causes general convulsions. The inhibitory effects are absent and the impulses irradiate to cause incoordinate contraction of all the muscles. The convulsions are stopped if afferent impulses are prevented from reaching the spinal cord. Chloroform converts excitation into inhibition and is thus antagonistic to strychnine.

Some of the phenomena of reflexes can be shown by junctional tissues other than those in the nervous system. Just as nicotine abolishes conduction at the synapse, so does curare abolish the transmission of the nerve impulse to the muscle. In the experiment showing that nerve fibres are not fatigued (p. 310), it can be shown that the fatigue is largely at the motor ending of the nerve. If the muscle which has ceased to respond to the stimulation of its nerve be stimulated directly it will contract showing that the muscle fibre is not completely fatigued. This demonstrates that the lack of response is due to fatigue of something which is not nerve and not muscle.

**Supernormal State.** If the nerve of a muscle-nerve preparation is stimulated by two stimuli at different time intervals apart, it can be shown that when the stimuli are close together it requires a stronger stimulus for the second one if it is to produce any response. At a certain stage of recovery it is found that the preparation is more easily excited. The second stimulus may be weaker than one that would be normally necessary to stimulate a resting preparation. This phenomenon is found only when there is a junctional tissue. It is not found in muscle alone or in nerve

alone, but it can be shown in a muscle-nerve preparation, and Fig. 153 shows the increase in excitability at a certain stage of recovery.

The existence of this supernormal state is not unrelated to the fact that reflexes may be more easily produced by repeated stimuli than by single stimuli.

The synapse appears to be a region of resistance at which a delay in conduction occurs. This resistance varies according to the

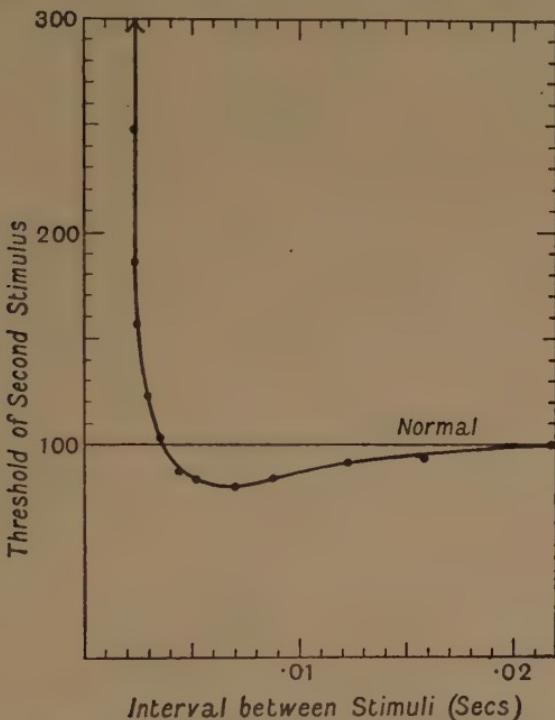


FIG. 153.—To show the Change of Threshold following an Excitation in a Nerve-Muscle Preparation of Crayfish (Keith Lucas in the *Journal of Physiology*, Cambridge Press).

Ordinates = thresholds of second stimuli in percentage of the threshold for a single stimulus.  
Abscissæ = time intervals between the two stimuli in secs. Between 0·004 and 0·015 secs. the excitability is above normal, as a stimulus below the threshold of a single stimulus is effective.

conditions of the experiment. Inhibition and facilitation produce their effect at the synapse and the synapse is more easily bridged by a series of stimuli.

The after-discharge of a reflex may be due to impulses arriving along different tracts. Those which have had to pass more synapses arrive later, so that the response continues after the stimulus has ceased.

The necessity of the central nervous system for reflex responses can be demonstrated by destruction of the spinal cord, after which

reflex responses cannot be obtained. The susceptibility of the synapse to lack of oxygen is shown by the rapid failure of reflex responses when the circulation of blood to the central nervous system is interfered with. The action of drugs on the synapse is exemplified by anaesthesia and by strychnine convulsions.

Spinal shock occurs when the spinal cord is cut across. Soon after the cord is cut reflex response is difficult or impossible to produce below the lesion. That the reflex mechanism is not destroyed is proved by the return of reflex response after a certain time interval. After total destruction of the cord the reflex responses do not return as the link between afferent and efferent paths is destroyed, whereas in spinal shock the structures are not destroyed but the ease of transmission of stimuli is interfered with, due to the destruction of the part of the cord where the cross section has been made.

When a "spinal animal" has recovered from spinal shock the reflexes may be exaggerated. This, as pointed out above, indicates a lesion of the upper motor neuron, i.e. cephalic to the parts involved in the reflex arc.

## CHAPTER XXIV

### THE SPINAL CORD

In our study of the reflexes we found that destruction of the spinal cord caused the abolition of reflexes, but that cutting the cord did not do so after the initial period of shock had passed off. This indicates that the spinal cord is essential for reflex action.

**Cross Section of Cord.** A transverse section of the spinal cord shows two kinds of structure, an inner H-shaped mass of darker colour called grey matter and an outer layer of lighter coloured material, called white matter. Histologically the grey matter consists of nerve cells and non-myelinated processes of nerves, whilst the white matter consists of myelinated nerve fibres. The central canal is contained in the crossbar of the H of grey matter.

The grey matter contains groups of nerve cells and the white matter can be marked out into conducting paths conveying different impulses, called tracts. The white matter is divided into three columns by the grey matter, namely dorsal, ventral and lateral.

The methods that are used to investigate the nervous system are :—

1. *Stimulation.* This method enables one to trace the conducting paths from one part of the nervous system to another. It is similar to the method of investigating the action of the roots of the spinal nerves.

2. *Section or Ablation.* By cutting or removing a portion of the nervous system certain effects may be produced. These effects may be due either to destruction of nerve cells or to interruption of conducting white fibres.

3. *Wallerian Degeneration.* When a nerve fibre is separated from its nerve cell the fibre degenerates. The changes that occur in the fibre are described on p. 311. In the central nervous system these changes may be recognized by Marchi's method which stains degenerating but not normal fibres. After the nerve fibres have degenerated the degenerated tracts may be recognized by Weigert's method, which consists in overstaining with haematoxylin, followed by bleaching. The degenerated nerve fibres are recognized because they are unstained, whilst the normal myelinated fibres are stained a dark blue-black. Owing to the absence of neurolemma on the

medullated fibres in the central nervous system regeneration does not occur.

4. *Degeneration Changes in the Nerve Cells.* When a nerve fibre is cut off from its cell the cell undergoes certain changes. These commence with chromatolysis, during which the Nissl granules break up and disappear. Later on the nerve cell atrophies. These changes in the nerve cells enable one to find the part of the nervous system which contains the nerve cells from which the cut nerve fibres have originated.

5. *Myelination or Embryological Method.* It has been found by Flechsig that the various nerve tracts become myelinated at different periods of growth. The times at which the myelin sheaths are formed correspond to the periods at which the paths become physiologically active. Thus it is possible to map out conducting paths according to the age at which the nerve fibres become medullated.

6. *Comparative Method.* An examination of the histological arrangement of the cells of the cerebral cortex by various observers has shown that the layers of cells and fibres show differences in different areas. The histological maps thus charted are compared with the results obtained by stimulation and ablation and with the special development or lack of development of special senses in different species of animals, e.g. the highly developed sense of smell of the sheep and the dog is correlated with an enlargement of the under surface of the temporal lobe of their brains (pyriform lobe).

7. *Pathological Records.* The results of injury and disease in men throw considerable light on the functions of the nervous system. These are really examples of cutting, ablation or stimulation experiments, but the processes are not so accurately controlled as in experimental methods. The importance of these records, in spite of less accurate control of the areas affected is that sensations can be more accurately determined and the " mentality " studied in a way that is impossible in animals.

**Effect of Cutting Dorsal and Ventral Spinal Roots.** In studying the reflex arcs we found that the dorsal root consisted of fibres which degenerated towards the spinal cord when the root was cut between the ganglion and the cord. The fibres when traced into the spinal cord are found to divide. One branch can be traced in the direction of the brain, the other is directed in the opposite direction. The cephalically-directed branch lies in the dorsal columns of grey matter. At first it is close to the dorsal horn of grey matter, but as it is traced towards the medulla it is pushed towards the mesial plane by fresh fibres entering from the more cephalic dorsal roots. Some of these fibres extend as far as the medulla. The caudally-directed branch can be traced for only

a few segments in an intermediate position in the dorsal columns.

Although this is all that is visible it can be shown that other fibres must pass into the grey matter. For instance, the occurrence of reflexes indicates that there must be some connection between the ventral and dorsal roots and results to be described later indicate that some fibres pass to the opposite side of the cord. Certain of these connections consist of branches from the nerve fibres, these branches being known as "collaterals."

On cutting the ventral roots degeneration occurs away from the cord, but certain cells in the ventral (and lateral) horn of grey matter show changes which indicate that they are the cells from which the nerve fibres of the ventral root arise.

**Effect of Section of the Spinal Cord.** When the spinal cord is cut completely across all connection between one part and the other is severed. Therefore all conducting paths are interrupted. Under these circumstances there is a condition of "shock" which varies in degree according to the complexity of the nervous system of the animal whose cord has been cut. After this stage has passed the reflex movements reappear, but there is no "voluntary" control of the parts supplied from the portion of the cord caudal to the point of section nor is there any sensation from these parts. This clearly indicates that the cord is a reflex and conducting organ. Destruction of the cord causes permanent loss of the reflexes because the connection between the dorsal and ventral roots is destroyed.

Subsequent to section of the spinal cord the white matter undergoes degeneration away from the nerve cells which give rise to the cut axons. Different areas of the white matter can be demarcated, as degeneration occurs in some groups of fibres in the cephalic and in others in the caudal direction. Thus we find that the cord is divided into tracts, some with their nerve cells on the cephalic side of the cut with fibres running caudally and others with nerve cells on the caudal side and with their fibres running in the cephalic direction : the former are called tracts of descending degeneration and the latter tracts of ascending degeneration. These various tracts can be traced through the nervous system, and they are most conveniently described by naming them so that the situation of their nerve cells forms the first part of the name and the part to which the fibres are distributed forms the second part, e.g. cortico-spinal tract from the cortex to the cord and spino-bulbar tract from the cord to the bulb.

The area which shows ascending degeneration is much greater than that which degenerates in the caudal direction. The former, as we shall see later, are tracts which convey impulses from receptor fibres, i.e. they are afferent fibres.

A much smaller area shows degeneration in the caudal direction. These fibres are mainly fibres conveying impulses from the brain towards effector organs, i.e. efferent fibres.

The various tracts have been demarcated by the methods mentioned above, and they will be briefly described here, but further evidence as to their function will be given later. The tracts are divided into long and short tracts. The former are those that extend throughout the greater length of the cord; the latter are those that extend over only a few segments of the cord.

**Descending Tracts.** In the lateral columns of the cord are two descending tracts. The larger of these lies opposite the base of the posterior horn. It contains fibres passing downwards from

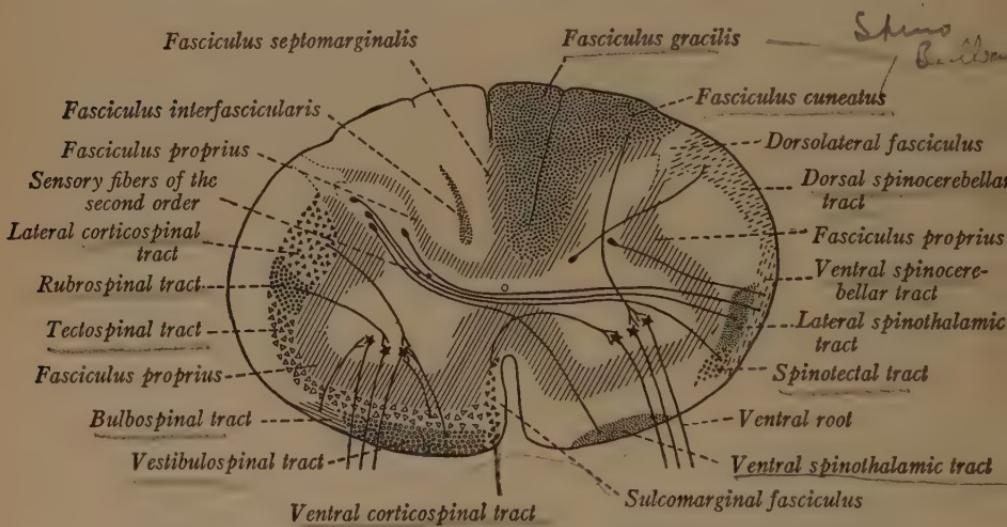


FIG. 154.—Diagram showing the Location of the Principal Fibre Tracts in the Spinal Cord of Man (Ranson).

Ascending tracts on the right side, descending tracts on the left.

the cerebrum of the opposite side with a few fibres from the cerebrum of the same side to regulate the activities of the voluntary muscles. It is called the lateral cortico-spinal tract. Immediately ventral to the lateral cortico-spinal tract is another descending tract known as the rubro-spinal tract. It conveys impulses from the red nucleus of the mid-brain to voluntary muscles.

There are other descending tracts, opposite the ventral horn of grey matter, known as the tecto-spinal, bulbo-spinal and vestibulo-spinal tracts. They convey impulses which probably exert some effect on the maintained contraction of cross striated muscle.

The dorsal columns contain fibres which have already been described as the cephalic branches from the dorsal roots; they are

called the *spino-bulbar* tracts. These fibres are frequently described as two tracts because they end at the caudal end of the medulla in two nuclei known as the *nucleus gracilis* and *nucleus cuneatus*. Some of the fibres of these tracts end at various levels of the cord but most of them pass to the above two nuclei from which a relay of fibres continues the pathway.

In the ventral columns is a descending tract confined to the cervical and thoracic regions of the cord. This is known as the *ventral cortico-spinal* tract, and it conveys impulses from the same side of the cerebrum towards the skeletal muscles. The fibres of this tract cross before connecting with the motor neurons.

In the dorsal columns is a short descending tract known as the *comma* tract. This consists of fibres already described as the caudal branches from the dorsal root.

**Ascending Tracts.** The outer surface of the lateral columns are occupied by two tracts. One occupying the region superficial to the lateral cortico-spinal tract is known as the *dorsal spino-cerebellar* tract, it conducts fibres from the spinal cord directly into the cerebellum; the other ventral to the dorsal spino-cerebellar tract is a mixed tract known as the *ventral spino-cerebellar* tract. It contains fibres from the grey matter of both sides of the spinal cord to the cerebellum.

On the ventral surface of the cord are two tracts known as the ventral and dorsal *spino-thalamic* tracts, containing fibres which pass from the cord to the optic-thalamus at the base of the cerebrum. Associated with this are some fibres which travel to the corpora quadrigemina, forming what is known as the *spino-tectal* tract.

The dorsal columns contain two tracts of a similar character. They contain fibres derived from the dorsal roots which run towards the cephalic end of the cord: they form the *spino-bulbar* tracts. Some fibres end in various levels of the cord, but a large number reach two groups of nerve cells known as the *nucleus gracilis* and *nucleus cuneatus*. These nuclei are situated at the lower end of the medulla and relay fibres, the greater number of which pass either to the cerebellum with the direct cerebellar tract or to the optic thalamus with the *spino-thalamic* tract.

There is a considerable area of white matter close to the grey matter which is not included in the above tracts. This is known as the "ground bundle," and it consists of short association tracts connecting various segments of the cord with each other. In order to show these tracts it is necessary to remove all the long tracts, after which it is possible to trace the short tracts when their fibres have been cut. The experiment is carried out in two stages. The preliminary stage is to make a complete transverse section of the

spinal cord and allow all the long tracts to degenerate and become absorbed. The final stage is either to cut several dorsal roots adjacent to the previous section or to transect the white matter a segment or two away from the original cut. Those fibres having their cells of origin in the severed dorsal roots or in the grey matter of the cord between two sections will degenerate. A few days later the animal is killed and the spinal cord stained by Marchi's method. The degenerating fibres will stand out against a background of normal and degenerated fibres; thus it is possible to trace the course of fibres originating in cells from a limited region of the nervous system. This is known as the method of *successive degeneration*.

**Effect of Section of One Lateral Half of the Spinal Cord.** Instead of the complete interruption obtained with complete section one finds a curious dissociation between afferent and efferent impulses (*hemiplegia*).

There is complete paralysis on the same side of the body (ipsi-

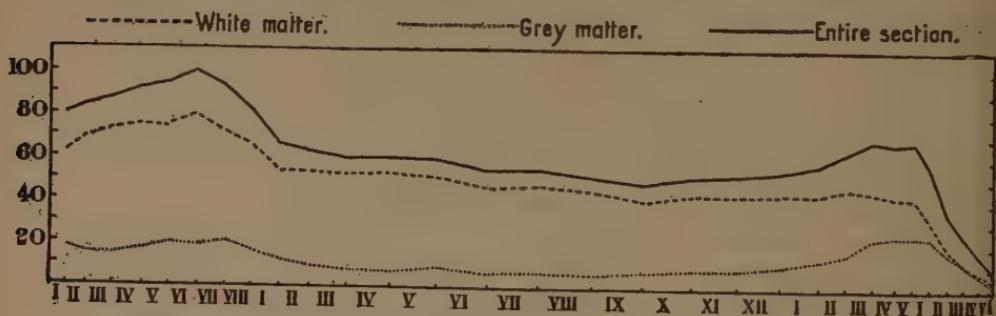


FIG. 155.—Curves showing the Variations in Sectional Area of the Grey Matter, the White Matter, and the entire Cord in the various Segments of the Human Spinal Cord (Donaldson and Davis).

(lateral) of all effector organs supplied from the cord below the point of section. The afferent impulses are divided so that loss of sensation occurs mainly on the opposite side (contralateral) for those parts of the body supplied from the cord several segments below the point of section. The sensations that are thus lost are those of pain, heat, cold and pressure; touch is affected to a lesser extent. On the same side of the body touch is interfered with to some degree. For a few segments below the level of section the sensations are interfered with and confused. The deduction from this curious result is that the efferent impulses in the cord pass down mainly on the side to which they correspond, but that sensory impulses soon after entering the cord cross the mid-line and pass up the contralateral tracts. The confusion near the level of section is due to interruption of fibres from both sides, i.e. those which have entered

from the same side before they cross and those that have entered from the opposite side after they have crossed. As touch sensations are affected on both sides of the body the fibres conveying touch sensations pass up partly crossed and partly uncrossed.

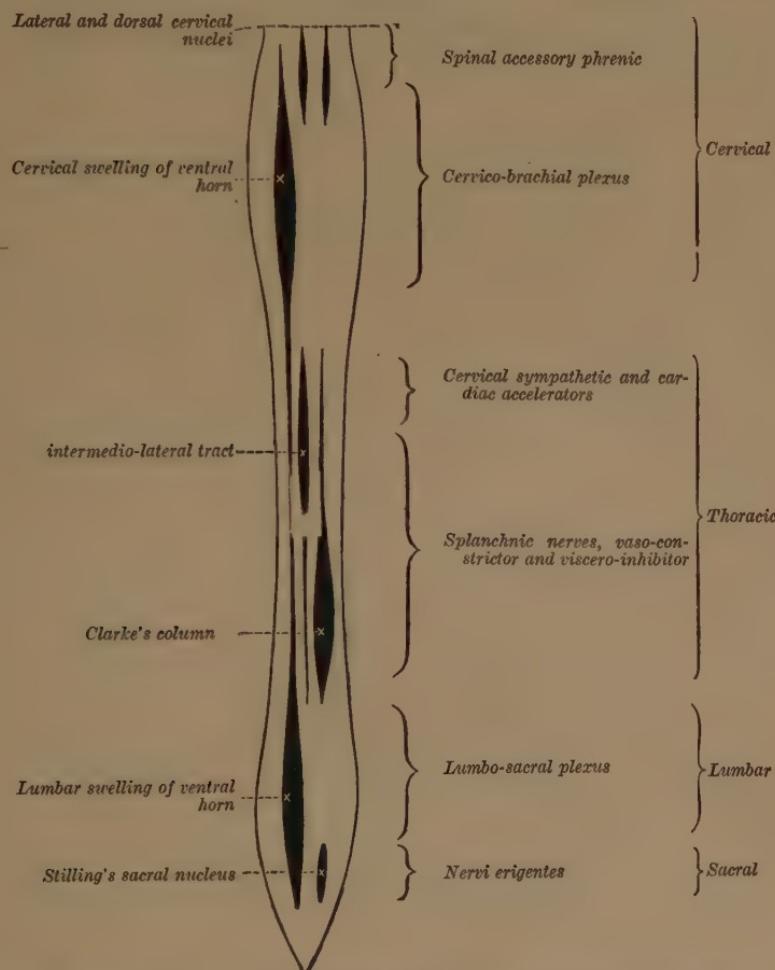


FIG. 156.—Side View of a Diagrammatic Section of the Spinal Cord.

To illustrate the distribution of the columns of nerve cells. The levels of origin of the principal nerves are indicated by brackets (from Waller's *Human Physiology*, Longmans, Green & Co.).

As we shall find out later many afferent paths are ipsilateral, but they are not sensory as they do not give rise to sensations.

On examining the distribution of white and grey matter throughout the length of the cord we find that the white matter increases in amount towards the cephalic end. This is obviously an expression

of the fact that the white matter largely represents connections between the brain and cord so that all the fibres must pass through the cervical region, but only those to the lumbar region pass through the lower dorsal region.

The increase in white matter is not uniform along the length of the cord, but it is relatively greater just above the cervical and lumbar regions because of the large number of connections required

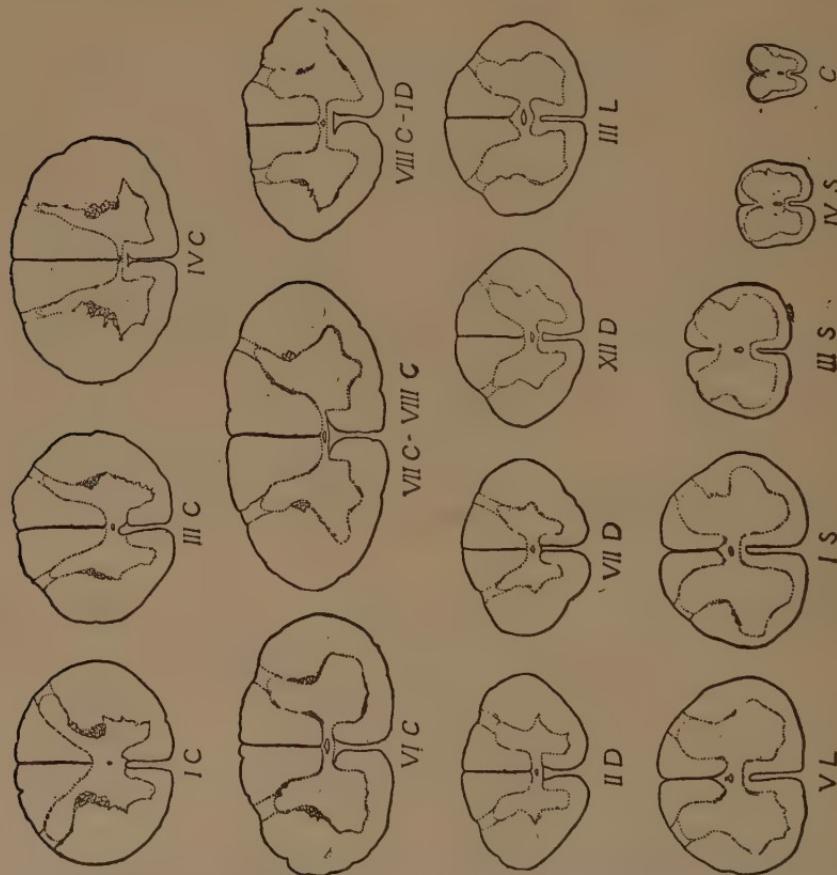


FIG. 157.—Outline Drawings of Sections through representative Segments of the Human Spinal Cord (*Ranson's Anatomy of the Nervous System*. W. B. Saunders Co.).

to link up the brain to the regions where the large nerves to the limbs are connected with the cord.

The area of each segment of the cord which is occupied by grey matter depends upon the number of nerve cells in that segment. The number of nerve cells is related to the number of afferent and efferent fibres entering or leaving the cord, hence we find enlarge-

ments of grey matter corresponding to the origins of groups of nerve fibres. The large efferent tracts to the arm and leg are responsible for the cervical and lumbar enlargements of the ventral horn. Above the entrances of the nerves of the lower limbs fresh neurons relay impulses from them to the brain, thus there is an enlargement of the gray matter at the base of the dorsal horn (Clark's column). In the thoracic region the lateral horn is enlarged

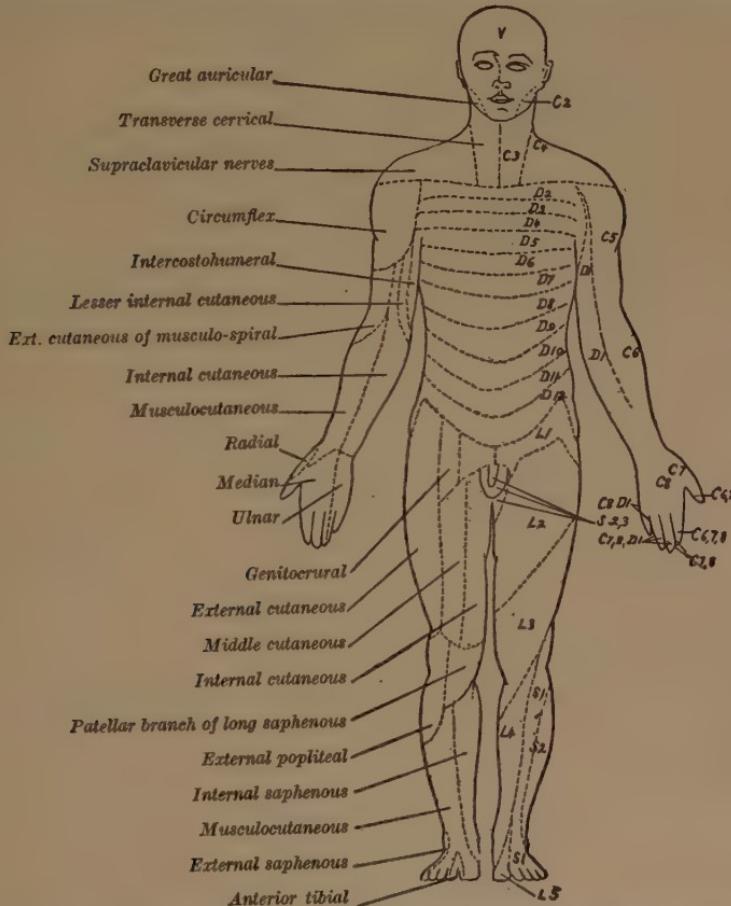


FIG. 158.—Sensory Root Fields on the Right, contrasted with the Areas of Distribution of Cutaneous Nerves on the Left (Ranson).

corresponding to the origin of the sympathetic nerves from this region. In Fig 156 are shown the enlargements of grey matter in different segments of the cord.

The influence of the relative amounts of white and grey matter on the shape of the cord is shown in Fig. 157.

The supporting framework of the central nervous system consists

of *neuroglia*. This is in the form of small cells with radiating branches.

The various segments (*metameres*) of the cord correspond to definite areas of the body surface. Owing to the growth of the limbs the areas represented by certain metameres have become spread over the surface of the limbs. By means of this distribution we can determine which part of the limb corresponds to the cephalic and which to the caudal side of an outgrowth which can be represented as growing out at right angles to the axis of the body.

The distribution of nerves does not correspond to the areas representing the metameres.

In Fig. 158 the nerve distribution is shown on one side of the body and that of the metameres on the other. These differences are important in the recognition of nerve injuries. By the distribution of the paralysis (motor and sensory) following a lesion we can determine in which part of the nervous system the lesion occurs.

In the same way a knowledge of the connections of various tracts in the nervous system is of use in determining the situation of growths or injuries.

In order to comprehend the full significance of the various tracts it is necessary to study the other portions of the nervous system. The functions of the various tracts will be described later when we know more about the other problems concerned in the nervous system.

## CHAPTER XXV

### THE CEREBRUM

In the study of the nervous system one is impressed by the process of sorting which is carried out. In the peripheral distribution of nerves one finds that both afferent and efferent fibres are contained in most nerves and that the distribution is to physiological units, e.g. muscle, gland or skin. The connection of these units to the nervous system is by the nerve roots, one of which contains only efferent and the other afferent nerve fibres. In the cord these are further sorted so that bundles of nerve fibres conveying similar kinds of impulses are collected into tracts which are less related to the parts of the body than to the kind of impulse conveyed by them.

When we study the most cephalic portion of the nervous system we find this principle well developed as the cerebrum represents functions and not primarily regions of the body. Each half of the cerebrum is linked to the opposite side of the body, i.e. the localization is contralateral.

The cerebrum consists of a central mass of grey matter consisting of the optic-thalamus, corpora striata, claustra lenticular and amygdaloid nuclei, i.e. one of each on each side known collectively as the basal ganglia. Overlying these ganglia is the cortex consisting of a superficial layer of grey matter lying on a mass of white matter.

#### Cortex

Superficially the cortex is divided into lobes by deep fissures and other shallower fissures divide each lobe into gyri. By these fissures the surface area of the grey matter is increased, thus allowing room for a larger number of nerve cells. In fact the degree of intelligence of an animal is proportional to the extent of complication of its brain by fissures.

The representation of functions in various parts of the cortex has been determined by a number of different experimental methods.

1. DIRECT STIMULATION is useful in showing from which parts of the cortex muscular movements can be produced. By this method it has been found that there is a motor area situated in the precentral gyrus. This area represents movements and thus

differs from the ventral horn of the spinal cord which represents muscles. The extent of cortex corresponding to an area of the body depends on the complexity of movement and not the mass of muscle involved, thus the area devoted to movements of such a small muscle as the tongue, is greater than that devoted to the large mass of muscles in the leg.

The arrangement of areas of the body in the motor area corresponds to the body inverted, but the face area is represented in its normal relations. Thus the upper part of the motor area represents the peroneal region, then succeed the areas for the leg, next the leg, trunk, arm and head.

Movements may be produced by stimulation of other parts of the cortex, but as we shall find later most of these are areas of sensory reception and the movements are more of a reflex nature. A special area for conjugate movements of the eyes is found in the inferior frontal convolution.

Stimulation gives more direct information than other methods, but positive results are limited to those areas which give motor responses.

2. REMOVAL of parts of the cortex in animals or the result of destruction due to disease in man leads to alterations in behaviour from which the function of the affected area may be surmised. This information is not so easy to assay as the movements that result from direct stimulation, but in conjunction with other methods it gives useful help. For instance, removal of the occipital lobe causes blindness as shown by the animal running into obstacles in its path. As direct stimulation of the occipital lobe causes movements of the eyes these two methods reinforce each other in indicating that the occipital lobe is concerned with vision. The results of disease are often more difficult to interpret than those of experimental lesions, but a number of localized lesions have been recorded accurately with the result that we describe certain parts of the cortex as being the parts that receive sensory impulses. Direct stimulation of sensory areas in the conscious human subject does not give rise to clearly recognized sensations (Cushing).

3. HISTOLOGICAL study of the cortex shows that the details of its structure vary in different parts. The general structure can be described as consisting of five layers as follows :—

(i) Outer molecular layer consisting of small transverse fibres (*I* in Fig. 159).

(ii) An outer nuclear layer consisting of small, medium and large pyramidal cells in that order from without inwards. The bases of the pyramids are directed inwards and the apices outwards. (*II* and *III* in Fig. 159.)

(iii) A granular layer consisting of a large number of small

stellate cells with well-marked nuclei, thus giving a granular appearance to this layer. (*IV* in Fig. 159.)

(iv) An inner molecular layer consisting of connecting nerve fibres and large pyramidal cells. (*V* in Fig. 159.)

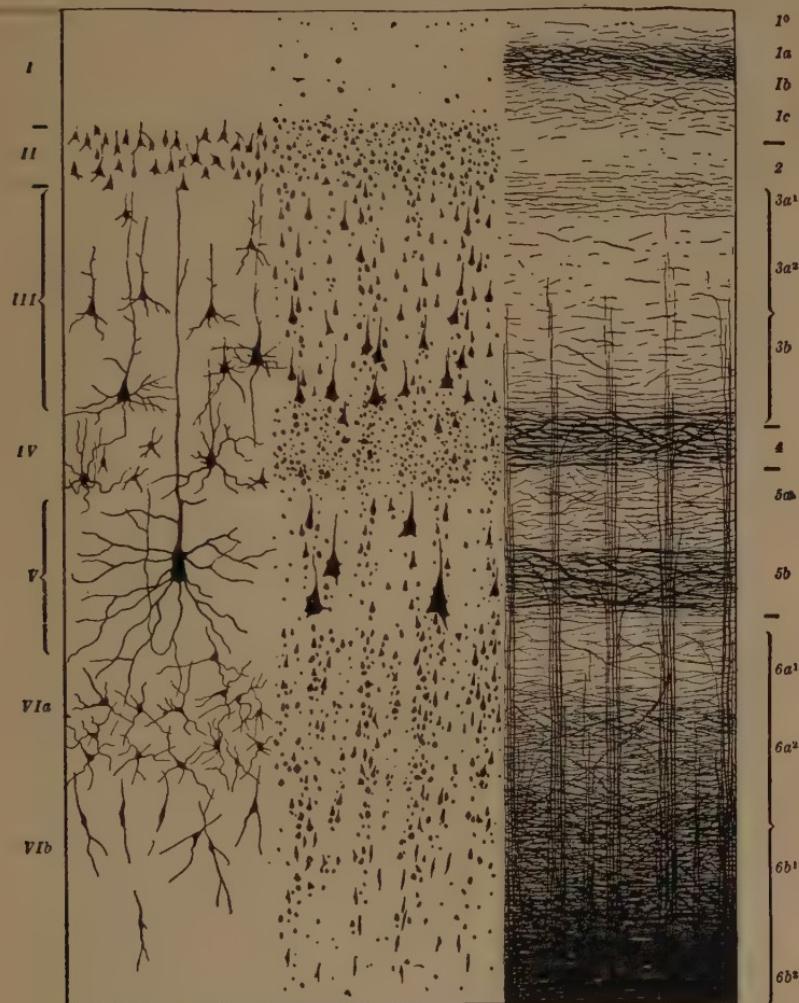


FIG. 159.—Diagram of the Structure of the Cerebral Cortex.

*I*, Molecular layer; *II*, layer of small pyramidal cells; *III*, layer of medium-sized and large pyramidal cells; *IV*, layer of small stellate cells; *V*, deep layer of large pyramidal cells; *VI*, layer of polymorphic cells; *3a<sup>1</sup>*, band of Bechterew; *4*, outer band of Baillarger; *5b*, inner band of Baillarger (Brodmann).

(v) An inner nuclear layer consisting of irregularly shaped (polymorphic) cells. (*VIa* and *b* in Fig. 159.)

Below these layers is the white matter of the cerebrum.

Variations in this structure occur so that it is possible to map

the cortex into areas. An example of a chart from such a survey is shown in Figs. 161 and 162. The variations in structure may be so marked that some indication of them may be seen by the unaided eye in free-hand sections of the cortex.

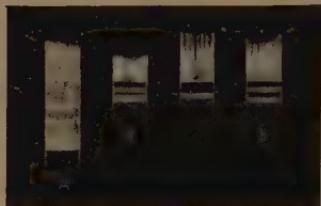


FIG. 160.—Diagram showing the Differences in Thickness and in the Arrangement of the Lighter and Darker Bands in the Human Cerebral Cortex in Different Regions as seen with the Naked Eye.

*A*, Motor cortex from anterior central gyrus; *B*, sensory cortex from the posterior central gyrus; *C*, visual cortex from the region of the calcarine fissure; *D*, auditory cortex from the anterior transverse temporal gyrus (redrawn after Elliot Smith).

The *main variations* are :—(a) In the motor area (*A* in Fig. 160) the inner molecular layer contains large pyramidal cells known as Betz cells. Each of these has arising from its base a large axon which runs towards the white matter below the inner nuclear layer. (b) In the sensory receptive areas the granular layer is greatly developed so that for instance in the posterior part of the occipital lobe it is divided into two by a layer of fibres: line of Gennari. (*C* in Fig. 160.) (c) In the frontal and parietal areas the outer layer of pyramidal cells is especially developed.

**4. ANATOMICAL CONNECTIONS OF THE CORTEX.** It is possible to trace the connections of the cortex with other parts of the nervous system. Where large numbers of medullated nerve fibres run in

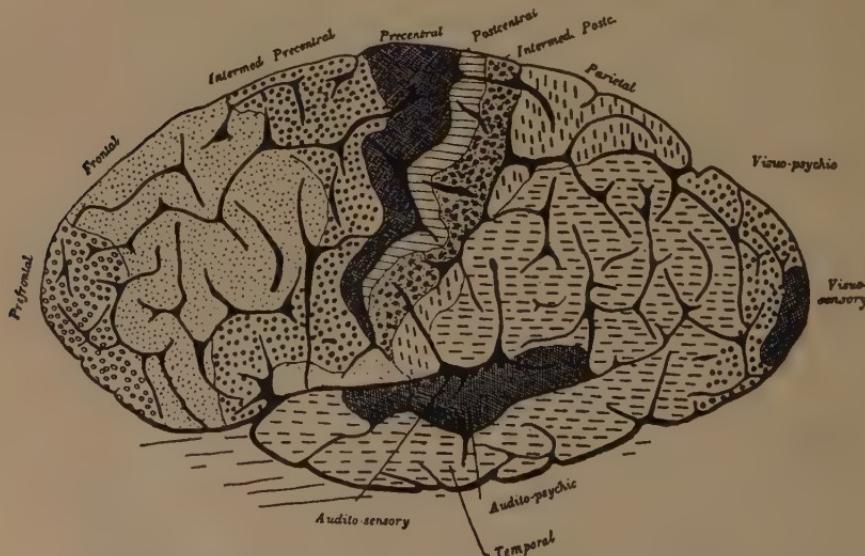


FIG. 161.—Outer Surface of Cerebrum to show the Areas of Different Histological Structure (Campbell).

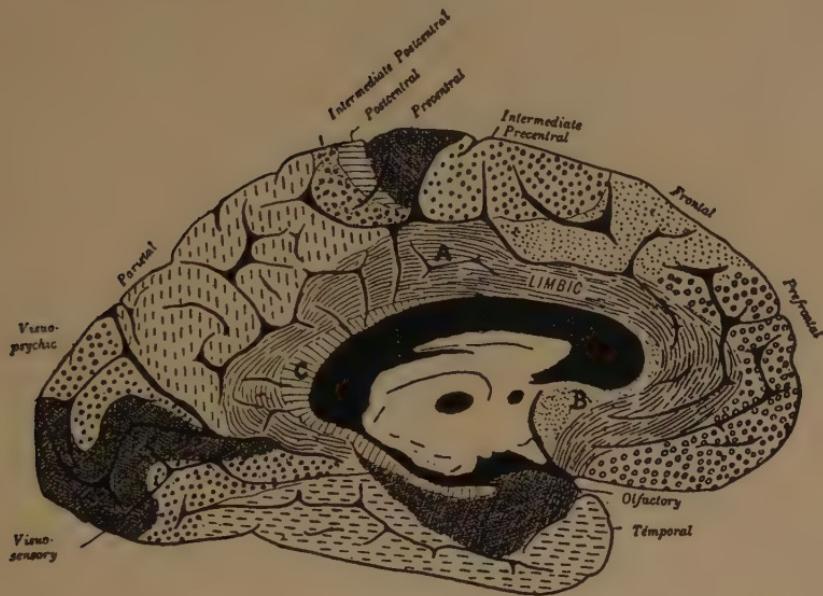


FIG. 162.—Medial Surface of Cerebrum to show the Areas of Different Histological Structure (Campbell).

the same direction the course of the fibres may be visible to the unaided eye. Therefore dissection may indicate some connections of the cortex with other regions.

Removal of an area containing cells will lead to Wallerian degeneration (see p. 311) of the fibres arising in that area. Cutting a nerve tract causes Wallerian degeneration of that tract away from the cells that give rise to it and at the same time it may cause chromatolysis of the cells from which the fibres arise. The course of the degenerating fibres shows the connections of the various parts. This method gives results which supplement those obtained by dissection, and it is especially useful for smaller tracts which would not be visible by dissection.

During embryological development different tracts acquire their myelin sheaths at different age periods according to the age at which they become functional. This is another means whereby the connections of the cortex with other parts may be traced. Charts made by this myelination method of Flechsig are shown in Fig. 163.

5. COMPARATIVE ANATOMY. By comparing the brains of different animals it is possible to obtain further evidence as to the localization of function in various parts of the cortex. In animals such as the sheep and dog, for instance, which have a more highly developed sense of smell than man, the inferior temporal area is

enlarged into a large pyriform area. Further stimulation of the corresponding area in the baboon causes movements of the nose.

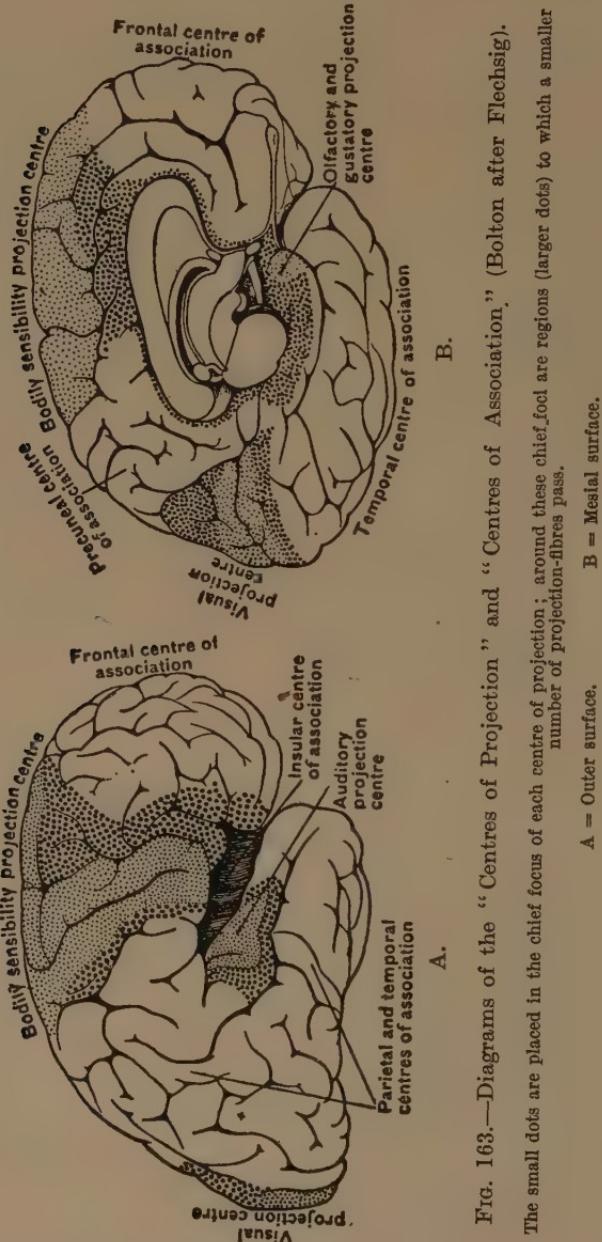


FIG. 163.—Diagrams of the “Centres of Projection” and “Centres of Association,” (Bolton after Flechsig).  
The small dots are placed in the chief focus of each centre of projection, around these chief foci are regions (larger dots) to which a smaller number of projection-fibres pass.

A = Outer surface.  
B = Mestial surface.

Therefore this area is believed to be the cortical area for smell.  
Figs. 164 and 165 show the areas that have been identified as

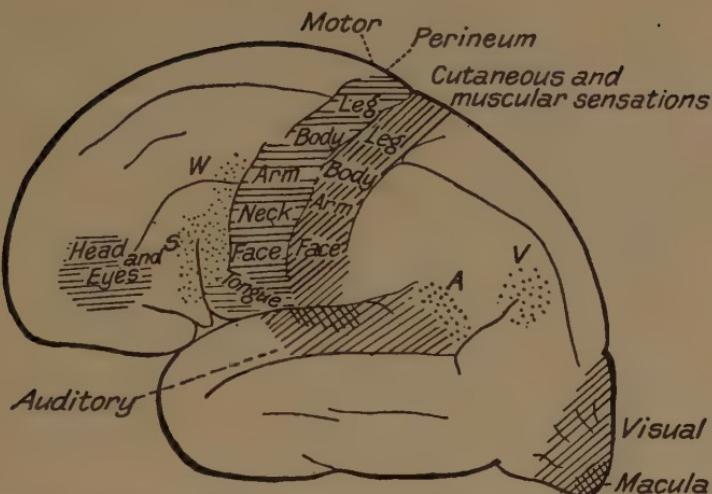


FIG. 164.—External Surface of Cerebrum to show the Localization of certain Functions in Definite Areas of the Cortex.

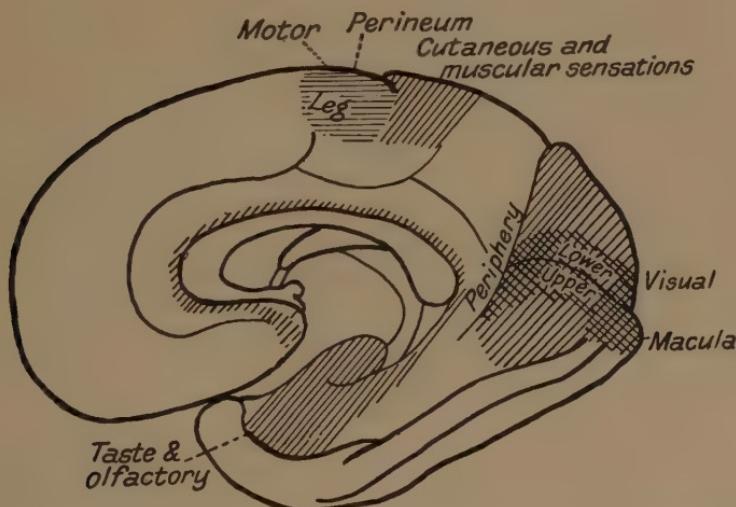


FIG. 165.—Mesial Surface of Cerebrum to show the Localization of certain Functions in Definite Areas of the Cortex.

Those areas from which only muscular movements have been evoked are marked by horizontal lines, whilst those which are believed to be associated with special afferent impulses are marked by oblique lines. Where a receiving area has been demarcated into a sensory and psychic region the sensory area is cross-hatched.

Parts of the cortex concerned with language are shown stippled: *V* = visual for the written word, *A* = auditory for the spoken word, *W* = for writing, and *S* = muscles for speech.

motor and sensory areas. Between these areas are so-called silent or association areas, particularly in the frontal and parietal lobes.

**Cell Layers.** The granular layer is always well developed in regions of sensory reception. Reception areas are generally divided into two parts, one of which has to do with the reception of sensations and the other with their interpretation. Thus at the posterior pole of the occipital lobe is the visuo-sensory area with a well-developed granular layer divided into two by the line of Gennari. Surrounding this is the visuo-psychic area which is believed to be the part of the cortex which interprets the sensations produced by the arrival of impulses at the visuo-sensory area.

The molecular and nuclear layers below the granular layer sometimes grouped as the infra-granular layer subserve the function of lower motor reflexes in relation to the obtaining of food, avoidance of danger and to the sexual functions. In the motor area the Betz cells are developed in the inner molecular layer.

The molecular and nuclear layers above the granular layer are likewise grouped as the supra-granular layer. They are believed to subserve the function of the higher mental processes. The evidence for this is partly phylogenetic as the pyramidal layer is more developed in man than in lower animals and this layer does not develop in man until the end of his embryonic stage. The thickness of the various layers are shown in Fig. 166, which compares the layers of the cortex in embryo, foetus and adult man with the cortex of the mole. It is clear that, relatively, adult man is characterized by the development of his layer of pyramidal cells. This layer is especially developed in the frontal and parietal regions. Further evidence is obtained from the fact that in dementia in which the intellectual functions have been lost the most marked histological changes are found in the layer of pyramidal cells. The cells are degenerated and the thickness of the supra-granular layer is diminished, and this decrease in thickness is best shown in the frontal and parietal areas.

**Jacksonian Epilepsy.** It was first suggested by Hughlings Jackson (1870) that the cortex of the brain represented definite localized parts of the body. He observed that irritation of certain parts of the brain caused attacks of epilepsy. These attacks commenced as rhythmical contractions of one group of muscles followed by tonic spasms. The contractions spread to other parts in a definite order which we now recognize as the anatomical representation of these parts in the motor area of the brain. After the attacks there may be either paresis or paralysis of the muscles which had been affected by the spasms. Sometimes the spasmoid stage does not occur, but only the paresis or paralysis. Similar effects may be found in sensory epilepsy where sensations of various

sorts may give warning of the attack, and after the attack anaesthesia of the area which seemed to initiate the sensations may occur. In the case of visual epilepsy the after-effect may be temporary blind-

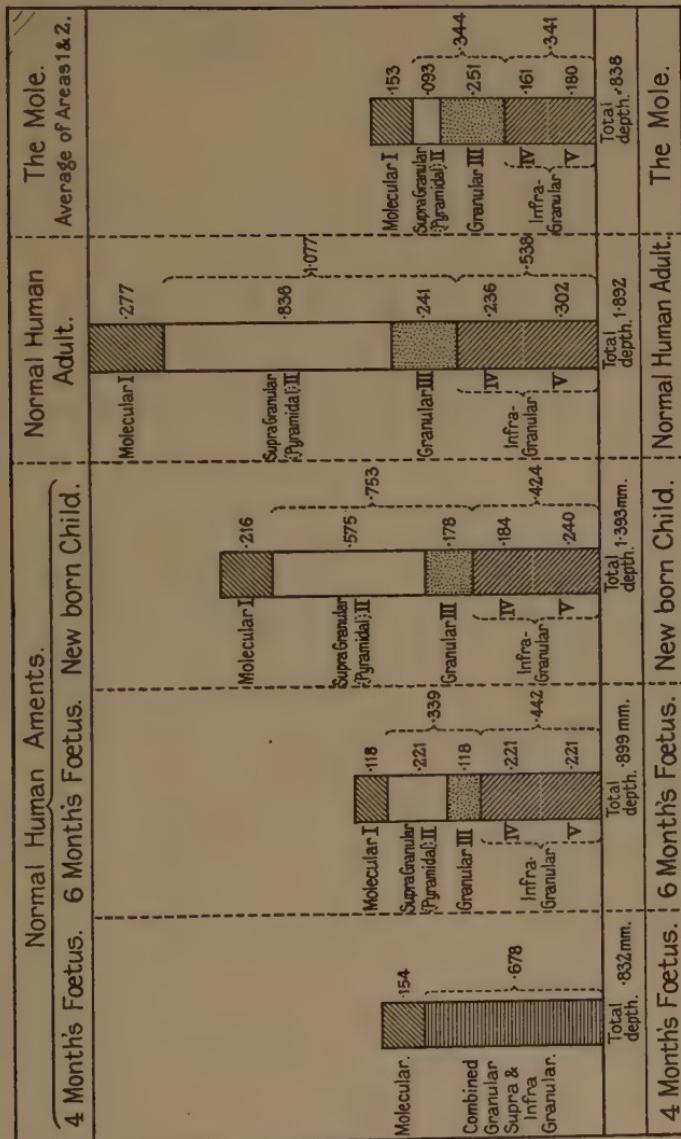


FIG. 166.—Showing approximately the Relative Depths of the Human Cerebral Cortical Layers at Various Stages of Development, and also those of the Mole (Watson).

ness of the corresponding visual field. Sometimes the preliminary motor or sensory stage may be very slight or absent and paralysis or loss of sensation may be the only indication of the attack. The importance of these "aura" is that they suggest the situation of some lesion in the cortex.

### Central Mass of Grey Matter

The grey matter below the cortex is more primitive than the overlying neo-pallium. It acts as a co-ordinating organ of less highly specialized nature than the cortex. We find that all sensory impulses reach the optic-thalami and related structure (e.g. corpora quadrigemina), where they give rise to consciousness of sensation. The sensation so aroused is of an indefinite pleasant or unpleasant nature, but for its accurate analysis as to quantitative effect and qualitative differentiation the impulse must be relayed to the cortex. Head describes the optic-thalami as possessing "affective tone."

The corpora striata probably have a controlling influence on temperature regulation.

Complete removal of the cerebrum causes a condition known as decerebrate rigidity. The muscles that antagonize gravity become contracted and remain stiff indefinitely. The decerebrate preparation shows no volition nor can it carry out any complicated reaction. It gives, however, excellent reflex responses.

If the cortex only is removed and the basal ganglia left the animal can walk, run, jump or sit up and behave in many ways like a complete animal. It does not show, however, the usual spontaneous movements of a normal animal.

These experiments indicate that the cerebrum exercises an inhibitory influence on the parts which produce decerebrate rigidity, and that basal ganglia can act as reflex centres enabling the animal to carry out complicated responses.

The importance of the cortex increases with the development of the animal. Thus removal of the cortex in fish produces less effect than in the frog, whilst in mammals there is a much greater difference in the behaviour of the animal than in birds. It is generally accepted that the cortex seems to be the last part of the brain to be developed and it is probably more important in man than in any other species.

The cerebrum is therefore the organ which is associated with consciousness. Every impulse which reaches the cerebrum need not give rise to a sensation, but it is necessary for the impulse to reach the cerebrum if it is to affect consciousness. It is the head ganglion of the extero-ceptive system.

The basal nuclei subserve the primitive form of consciousness known as affective tone, but for accurate comparison and discriminative action the impulses must be relayed to the cortex.

## CHAPTER XXVI

### THE CEREBELLUM AND BRAIN STEM

**Cerebellum.** We have seen that removal of the cerebrum leads to a spastic condition of the muscles. Removal of the cerebellum leads to disorder of muscular contractions, and an animal on which this experiment has been performed shows this muscular disorder by its staggering uncertain gait. In the case of a dog, its movements may be recorded by dipping each of its feet into a different dye and causing the animal to walk across a piece of paper. Fig. 167 shows the footprints of a normal dog, whilst Fig. 168 shows the effect of removal of a portion of its cerebellum on its movements.



FIG. 167.—Footprints of Normal Dog.

*p*, walking; *g*, galloping (Luciani, from Sherrington in Schafer's *Text-Book of Physiology*. Oxford Medical Publication.)

Removal of the cerebellum is said to produce paratonia, parasthenia and astasia. Removal of half the cerebellum affects the muscular movements of the same side of the body, thus contrasting with the cerebrum in showing ipsilateral and not contralateral representation. After such removal the contralateral side shows normal activity whilst the ipsilateral side is weak, hence the normal side moves further with the result that the animal tends to travel in a circle. It also assumes characteristic attitudes due to unequal muscular contraction.

The cerebellum consists of a central mass of grey matter embedded in white matter and on the surface is a cortex. As the cerebellum consists of a series of lamina the surface area of the cortex is much greater than if it were not so divided. Localization of function in it is not so accurately defined as in the case of the cerebrum : the

whole organ regulates muscular movements. The median unpaired parts of the cerebellum probably regulate bilateral movements (Bolk).

The HISTOLOGICAL STRUCTURE of the cortex shows two layers resting on the white matter. The outer layer consists of fibres forming a molecular layer, whilst the inner layer consists of cells forming a nuclear layer. At the margin between the two layers

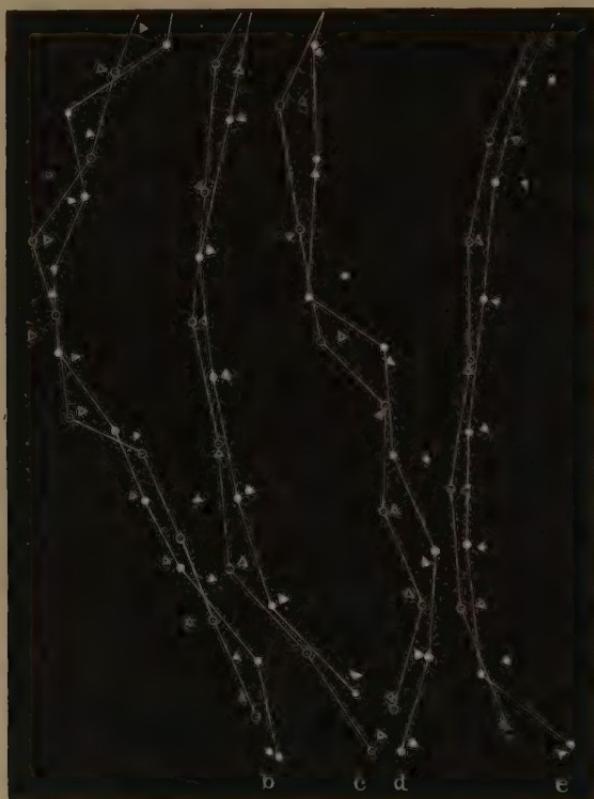


FIG. 168.—Footprints of a Dog after Ablation of the Middle Lobe of Cerebellum (Luciani, from Sherrington in Schafer's *Text-Book of Physiology*).

b, nine days after the operation; c, eleven days after the operation; d, fourteen days after the operation; e, eighteen days after the operation, animal blindfolded.

are special large flask-shaped cells known as Purkinje cells. The axons of these cells pass inwards to reach the central mass of grey matter, whilst the dendrons run outwards in a single plane like an espalier-trained fruit tree. In the molecular layer they are in contact with afferent impulses from various parts of the body. A few small nerve cells in the deeper part of the molecular layer form what are called basket cells.

The granular layer contains numerous small neurons. These small nerve cells form synapses with the terminal branches of axons which probably reach the cerebellum via the restiform body. These form what are called *mossy fibres*. The axons of the granular cells pass outwards to the molecular layer where they form a T-shaped branching so that the two branches run parallel to the surface of the cortex.

Entering the cortex are other axons which probably reach the cerebellum via the brachium pontis. These pass straight through the granular layer to be associated with the dendrons of the Purkinje cells. They are called *climbing fibres* owing to the ivy-like way in which they cling to the Purkinje cell processes.

The central mass of grey matter or *dentate nucleus* receives the axons of the Purkinje cells and sends out axons by the superior cerebellar peduncle to the cerebrum, red nucleus and nuclei in the pons and medulla.

**Brain Stem.** Linking up the cord, cerebrum and cerebellum is a central axis consisting of medulla oblongata, pons varolii and mid-brain, in which the tracts of white fibres undergo rearrangement and special masses of grey matter occur.

The medulla is continuous with the cord, and in it are found the terminations of the dorsal columns in the nuclei gracilis and cuneatus, the decussation of the motor tract, the decussation of the sensory tracts (or fillet), the opening of the central canal on its posterior

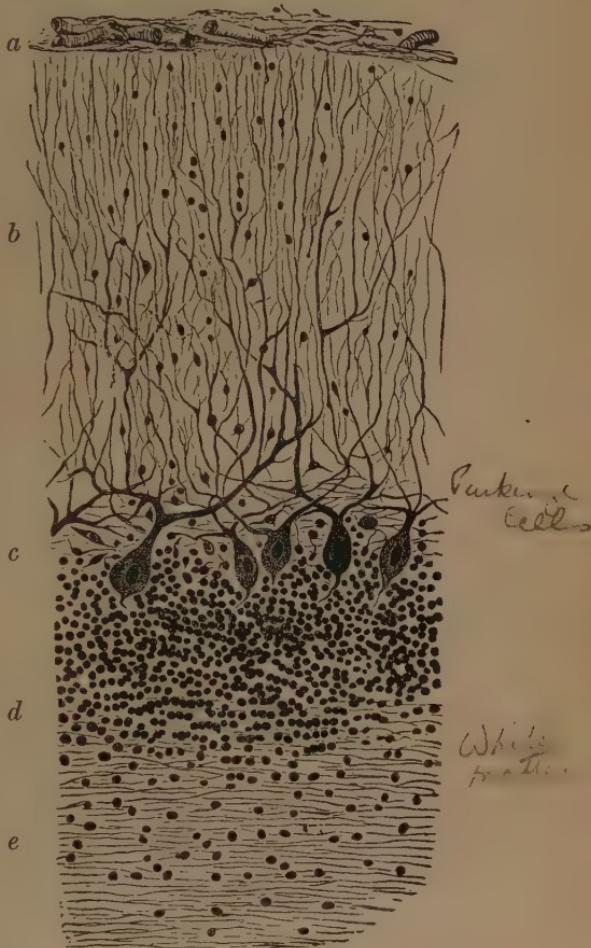


FIG. 169.—Section of Cerebellar Cortex  
(Sankey, from Quain's Anatomy).

a = pia mater, b = molecular layer, c = cells of Purkinje, d = granule layer, e = white matter.

aspect, the olivary nuclei and the inferior cerebellar peduncles or restiform bodies.

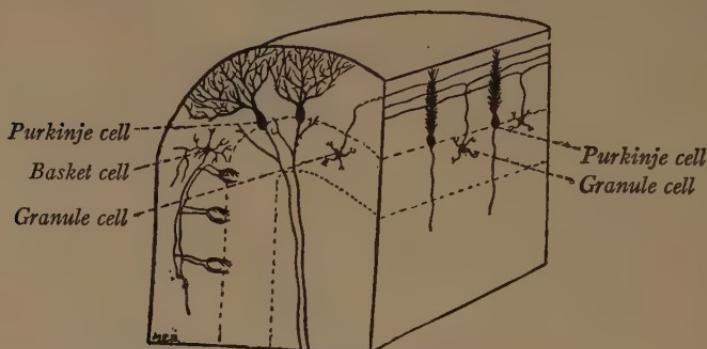


FIG. 170.—Diagrammatic Representation of the Structure of the Cerebellar Cortex as seen in a Section along the Axis of the Folium (on the right), and in a Section at Right Angles to the Axis of the Folium (on the left) (Ranson).

*The pons can be recognized by the large numbers of transverse*

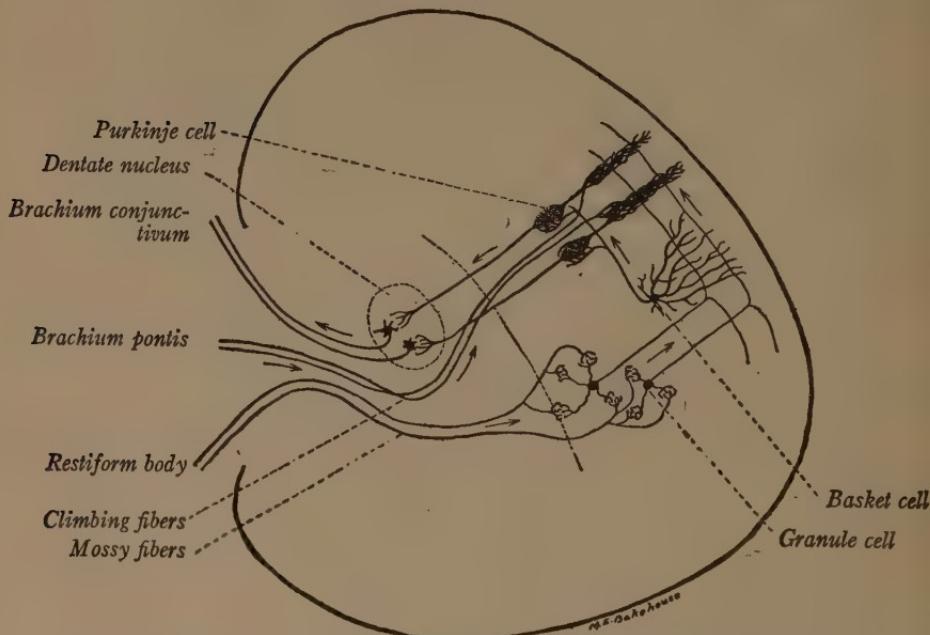


FIG. 171.—Diagram to illustrate the probable Lines of Conduction through the Cerebellum (Ranson's *Anatomy of the Nervous System*. W. B. Saunders Co.).

fibres which pass round it to form the middle cerebellar peduncles.  
*The mid-brain contains the crura cerebri, the substantia nigra,*

the red nuclei, the superior cerebellar peduncles, and the corpora quadrigemina.

Running the whole length of the brain stem is the grey matter continuous with that in the cord. The nuclei in this grey matter are related to the series of cranial nerves, from the third to the twelfth inclusive, which are connected with the brain stem.

The nuclei of origin of the cranial nerves have been traced by histological methods and their situations are shown in Fig. 172 A and B.

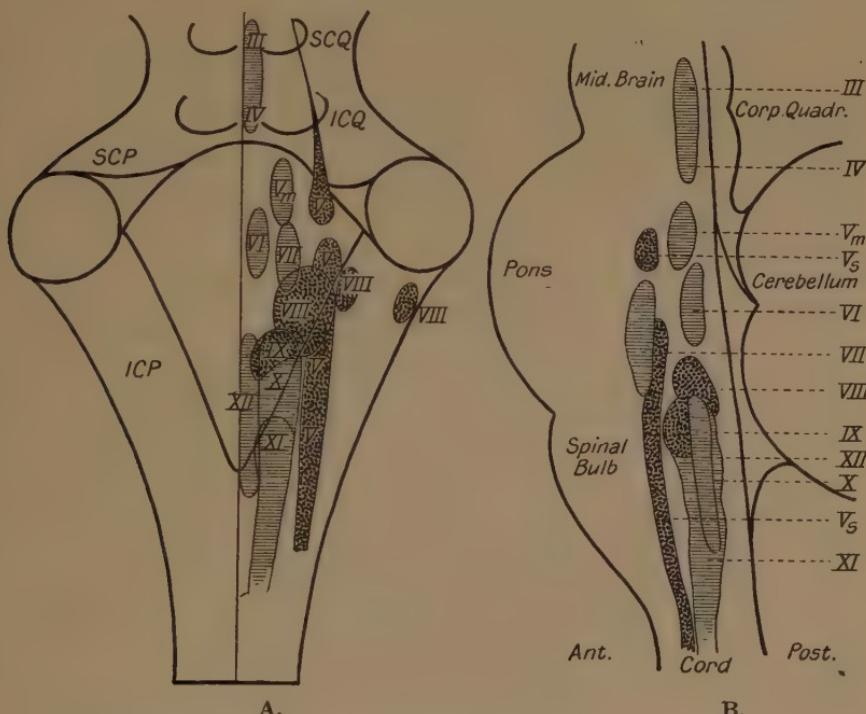


FIG. 172.—Diagrams to show the Bulbar Nuclei of the Cranial Nerves (Flack and Hill after Erb).

A. Posterior aspect of the fourth ventricle exposed by removal of the pons and cerebellum. Motor nuclei indicated by horizontal lines, sensory nuclei by dots. Median group of motor nuclei, *III, IV, VI, XII*. Lateral group of motor nuclei, *V<sub>m</sub>, VII, X, XI*. Sensory nuclei, *V<sub>s</sub>, VIII, IX*.

B. Lateral view of right half of bulb and pons. The lateral group of motor nuclei, *V<sub>m</sub>, VII, X* and *XI*, lie further from the surface of section than the median group *III, IV, VI* and *XII*.

In the medulla the central canal of the spinal cord opens on the dorsal surface. This causes the grey matter representing the dorsal horn to be displaced laterally whilst that corresponding to the ventral horn remains central. Because of this alteration in the position of the grey matter we expect the efferent nuclei to be situated near the mid-line and the nuclei for the efferent fibres to be more lateral. In general this is the case.

**Nuclei for Purely Efferent Nerves.** The purely motor nerves to striated muscles arise from a line of nuclei situated in the mid-line.

*Third Nerve.* The nucleus for this nerve lies ventral to the cerebral aqueduct at the level of the superior colliculus.

*Fourth Nerve.* The nucleus for this nerve lies ventral to the cerebral aqueduct at the level of the inferior colliculus.

*Sixth Nerve.* The nucleus for this nerve lies in the floor of the middle of the fourth ventricle.

*Eleventh Nerve.* The fibres of this nerve are connected to a series of nuclei which are situated externally to the line of the nucleus of the twelfth nerve. One group of fibres arises in conjunction with the tenth nerve from the dorsal nucleus of the tenth nerve and the nucleus ambiguus; the remaining groups originate from a series of nuclei extending down the lateral horn of grey matter of the first five or six segments of the cord. (See top of Fig. 156.)

*Twelfth Nerve.* The nucleus for the hypoglossal nerve is in the floor of the caudal end of the fourth ventricle.

**Nuclei for Mixed and Purely Afferent Nerves.** These lie lateral to the purely efferent nuclei. The afferent fibres arise in ganglia outside the central nervous system, but the fibres terminate in connection with cells forming the nuclei for these nerves.

*Fifth Nerve.* The motor root for this nerve arises from a nucleus lateral to the nuclei of the purely efferent nerves and intermediate in position between the nuclei of the fourth and sixth nerves.

The sensory nucleus for this nerve forms a continuous column from the level of the superior colliculus to the spinal cord. It lies lateral to most of the other nuclei, and its broadest part is close to the nucleus of its motor root.

*Seventh Nerve.* The motor nucleus for this nerve lies in line with that of the fifth nerve, but caudal to the nucleus of the sixth nerve.

The sensory nucleus lies low down near the caudal end of the medulla (*Tractus solitarius*).

*Eighth Nerve.* This is purely afferent, consisting of two divisions.

*Vestibular Portion.* Some of the fibres of this branch run directly into the cerebellum. The remainder terminate in the principal, lateral, superior and spinal vestibular nuclei forming a large area at the lateral region of the fourth ventricle.

*Cochlear Portion.* The fibres from this nerve end in the ventral and dorsal cochlear nuclei which are respectively ventral and dorsal to the restiform body.

*Ninth Nerve.* The efferent portion arises mainly from the nucleus ambiguus, which it shares with the tenth and eleventh nerves. It lies in line with the efferent nuclei of the fifth and seventh nerves,

but in the caudal region of the medulla. Its afferent portion ends in close relation to that of the seventh nerve (*Tractus solitarius*).

*Tenth Nerve.* The efferent fibres arise from the nucleus ambiguus and the dorsal nucleus of the tenth nerve which lies between the nucleus ambiguus and the nucleus of the twelfth nerve. The afferent fibres in the tractus solitarius with those of the seventh and ninth nerves end in the spinal tract of the fifth nerve.

The function of the grey matter of the medulla is, like that of the spinal cord, to regulate reflexes, but these are reflexes which have more relation to the general interests of the animal than have those in the cord. In order to carry out this function the brain stem exercises an inhibitory control over the cord. In the medulla are found the large so-called vital centres regulating the heart, circulation and respiration. Experimental evidence for this statement is given by the fact that if the medulla is cut off from the cord the respiration stops and if artificial respiration is maintained there is a marked fall in blood pressure. Section of the brain stem above the medulla does not cause stoppage of the respiration or a fall of blood pressure. By such methods it has been ascertained that part of the respiratory centre is in the medulla at about the level of the calamus scriptorius, which is close to the endings of the tenth nerves which bring afferent impulses from the lungs, circulatory organs and alimentary canal.

Destruction of the medulla causes death, hence the use of the term vital centres.

### TRACTS IN BRAIN STEM

In order to link up the various parts of the nervous system we will proceed to describe the course of the various tracts to and from the cord so that when we have done this the various parts already mentioned will be seen in their proper setting.

### THE CORTICO-SPINAL TRACTS

These tracts (see Fig. 173) arise from the Betz cells in the motor area whence they converge, forming the corona radiata, to pass through the genu and ventral part of the dorsal limb of the internal capsule. In this situation the fibres have become rotated through  $90^\circ$  so that the fibres for the head are ventral and those for the peroneal region are dorsal.

*Internal Capsule.* Ventral to the cortico-spinal fibres the internal capsule contains fronto-pontine fibres and dorsal to the pyramidal fibres are sensory fibres.

It is because all these important fibres are so close together at this point that a slight injury can produce such striking results.

From the internal capsule the cortico-spinal fibres pass to occupy the middle three-fifths of the crura cerebri the lateral fifth of which

contains temporo-pontine fibres, and the medial fifth fronto-pontine fibres. A group of motor fibres from the cortex to the motor nuclei in the pons separate at the inner border of each crus. These convey impulses from the motor area for the muscles of the face.

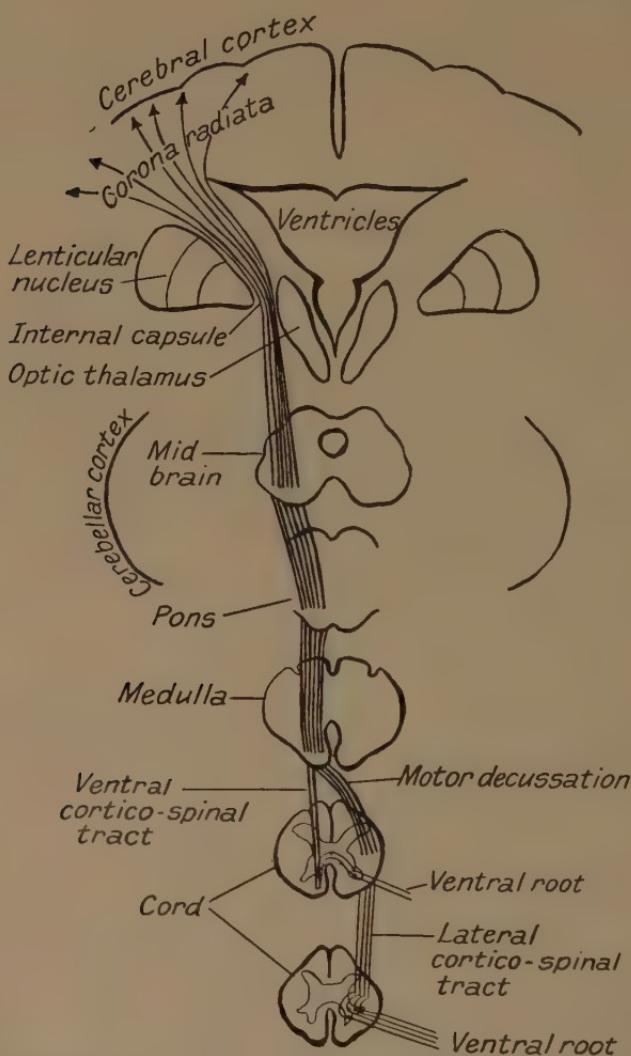


FIG. 173.—Diagram showing Course of Cortico-spinal (Motor) Tracts.

In the pons the cortico-spinal tracts lie near the ventral border, being broken into small bundles by the transverse fibres of the pons.

In the medulla the cortico-spinal tracts form the pyramids and

at the caudal end of the medulla the majority of the fibres cross, cutting through the continuation of the anterior horns to reach the lateral columns where they form the lateral cortico-spinal tracts. A small number of the cortico-spinal fibres do not cross in the medulla, but they pass directly into the cord as the ventral cortico-spinal tracts. The fibres of the latter cannot be traced beyond the upper thoracic region and they cross in the cervical region of the cord by passing through the anterior white commissure.

### SENSORY TRACTS

All sensory tracts pass to the optic thalamus and related structures, hence the various tracts in the cord must be traced to this region of the brain. The spino-thalamic and spino-tectal tracts which, in the cord, are situated near the surface opposite to the ventral horn of grey matter pass inwards to lie near the medial plane dorsal to the cortico-spinal tracts. Near the caudal end of the medulla these tracts are joined by fibres conveying touch sensations which have passed through the cord in the dorsal columns. These fibres are relays from the nuclei gracilis and cuneatus in which the fibres of the dorsal columns terminate; they join the fibres of the spino-thalamic and spino-tectal tracts by passing medially and ventrally to form the sensory decussation, which lies just cephalic and dorsal to the motor decussation. As the other sensory fibres have crossed in the cord all the sensory fibres in the brain stem therefore show contralateral representation. The union of the various sensory tracts forms the lemniscus or fillet. In the brain stem this is joined by fibres from the nuclei of the cranial nerves of which the larger number are contributed by the cochlear branch of the eighth nerve.

In the medulla the lemniscus lies behind the cortico-spinal tract but higher up it passes laterally. The spino-tectal tract with fibres which have joined it mainly from the cochlear branch of the eighth nerve, separates as the lateral lemniscus, bends dorsalwards to lie on the outer margin of the brachium conjunctivum. The lateral lemniscus passes mainly to the inferior colliculus. The spino-thalamic tracts with the fibres from the sensory decussation forming the medial lemniscus end in the optic thalamus where there is a relay. The axons from the cells in the optic thalamus pass by the dorsal part of the internal capsule to the post-central convolution in the parietal lobe.

### PROPRIOCEPTIVE TRACTS

The afferent fibres which convey the impulses necessary for the co-ordination of the movements of the body pass to the cerebellum

by the three peduncles known as the restiform body, the brachium pontis and the brachium conjunctivum.

The uncrossed or ipsilateral fibres of the dorsal columns end at the nuclei gracilis and cuneatus. The exteroceptive fibres of touch

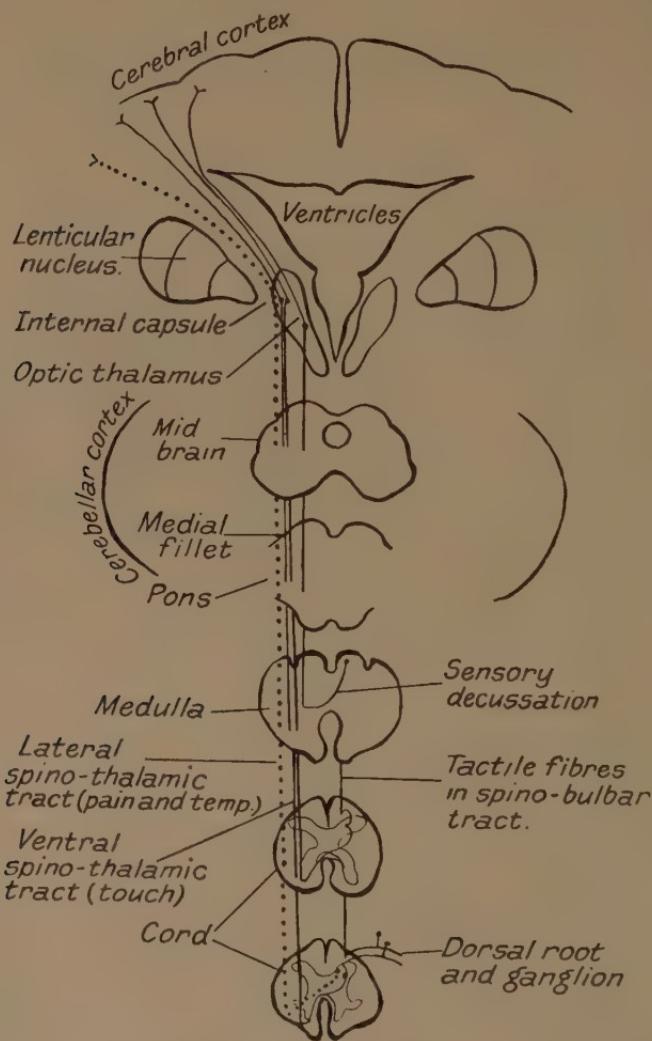


FIG. 174.—Diagram showing Course of Afferent Tracts for Cutaneous (Exteroceptive) Sensations.

are segregated, forming the sensory decussation, whilst the proprioceptive fibres, after a relay at the two nuclei pass to the restiform bodies as arcuate fibres. Some form dorsal external arcuate fibres to the same side; others pass ventrally, cross to the opposite

side and form ventral arcuate fibres to the opposite restiform body and still others form internal arcuate fibres to the opposite side. A certain number of fibres pass to the olfactory nuclei.

Thus the proprioceptive fibres from the dorsal columns pass into

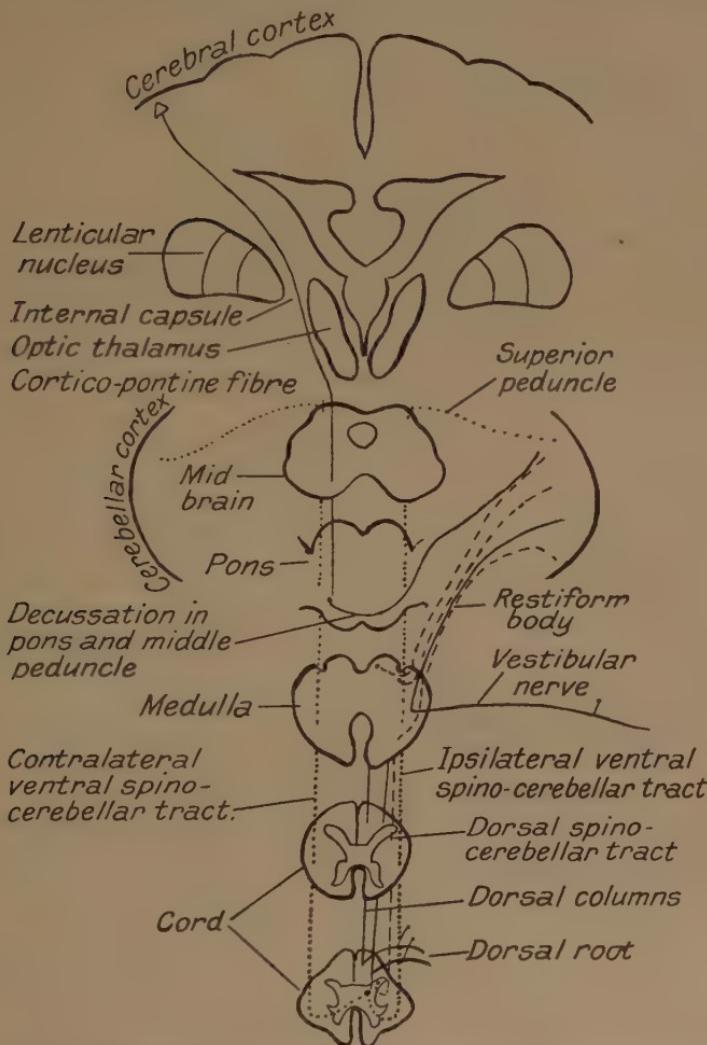


FIG. 175.—Diagram showing Course of Tracts running to the Cerebellum (mainly Proprioceptive).

the restiform bodies showing both ipsilateral and contralateral representation.

The fibres of the dorsal spino-cerebellar tracts pass directly dorsally into the ipsilateral restiform body.

In addition to these fibres the restiform bodies contain fibres from the cranial nerves, the larger number of which are from the vestibular portion of the eighth nerve.

The fibres of the ventral spino-cerebellar tracts which are partly ipsi- and partly contra-lateral pass through the medulla and pons. In the mid-brain they pass dorsally to the brachium conjunctivum. Here they are in relation with fibres from the cerebrum and with return-fibres from the cerebellum which will be described later.

The brachium pontis contains fibres from the various nuclei in the brain stem. Some of these are relay fibres for impulses from the cerebrum.

*Medial Longitudinal Bundle.* This consists of a group of connecting fibres linking up the nuclei concerned with movements of the head and eyes. Therefore it runs just beneath the grey matter of the floor of the fourth ventricle near the mid line from just below the third ventricle to the spinal cord, i.e. from the nuclei of the nerves to those of the spinal accessory nerve.

#### SUBSIDIARY MOTOR TRACTS

In addition to the cortico-spinal tracts there are other motor tracts, such as the rubro-spinal and vestibulo-spinal.

*The Rubro-spinal tract* is linked with the cerebrum by fibres which cross from the contra-lateral half of the cerebrum to the ipsi-lateral half of the cerebellum. These pass in by the brachium conjunctivum. Fibres pass out of the cerebellum by the brachium conjunctivum which cross to the contra-lateral cerebral hemisphere. After crossing, these fibres send collaterals to the red nucleus. Thus the cerebrum and cerebellum are connected so that their activities are correlated. As the cerebrum represents the opposite side of the body and the cerebellum the same side, the crossing of each set of fibres is necessary. The red nucleus forms a relay by which impulses may be sent down to the cord, and as the collaterals are contra-lateral having got back to the same side as the fibres from the cerebrum the fibres from the red nucleus must cross again, which they do as soon as they leave the nucleus. The rubro-spinal tract passes through the pons and medulla; in the cord it lies just ventral to the lateral cortico-spinal tract.

*The Vestibulo-spinal tract* arises in fibres mainly from Deiter's nucleus which pass caudalwards to the ventro-lateral white matter of the cord.

The above two tracts are supposed to convey impulses in relation to maintained contraction and tone. If the rubro-spinal tract is an accessory motor tract from the cerebrum it is indirect, involving a journey for the impulses to the cerebellum and back, with a triple

crossing, one on the way to the cerebellum, one on the way back, and a third after leaving the red nucleus.

The description here given is that of the main tracts, but it must not be forgotten that the actual paths are not so sharply defined. All parts of the nervous system are linked so that it can act as a whole and collaterals run from one part to another. The tracts herein mentioned will serve as a guide to the actions of the nervous system described in the following chapters.

## CHAPTER XXVII

### THE AUTONOMIC NERVOUS SYSTEM

When we study the action of the nervous system we find that there is a distinction between those afferent impulses which produce distinct conscious sensations and those which primarily are of use in correlating movements. Similarly we find that there is a broad distinction between those efferent impulses which control the striated muscles and those which control the non-striated muscles and glands. The former are known as voluntary, and the latter as involuntary.

The involuntary impulses are carried by a special set of nerves which form the sympathetic nervous system, the tectal and the bulbo-sacral outflow. In general the sympathetic and bulbo-sacral systems innervate the same structures but they act on them to produce opposite effects, and for the harmonious activity of the body they must act reciprocally. It will be simpler to describe the sympathetic system first.

**Sympathetic Nervous System.** The sympathetic system consists essentially of the two chains of sympathetic ganglia, one on each side of the spinal column and certain outlying ganglia connected with them.

These ganglia are connected with the spinal nerves by two different sorts of nerve fibres.

From the second dorsal to the third lumbar nerves white rami pass from the spinal nerves to the corresponding sympathetic ganglia. These represent connector neurons in the nervous system, and they arise from cells in the lateral horn of grey matter. It is because of these cells that the lateral horn is better developed in this region of the cord than in other regions.

The white rami consist of myelinated nerve fibres which end in the ganglia of the sympathetic system, hence they are known as preganglionic fibres. From these ganglia arise non-medullated fibres which pass to the distribution of the sympathetic system. In the course of each impulse there is only one relay, so we can call the non-myelinated fibres post-ganglionic fibres. Although there is only one cell station in each peripheral path, either a pre- or post-ganglionic fibre may give off collaterals. Therefore the

number of fibres to reach the peripheral structures is much greater than the number of fibres that pass out by the white rami.

As some of the structures innervated through the sympathetic system are more conveniently reached through the spinal nerves we find that each spinal nerve receives a supply of post-ganglionic non-myelinated fibres known as the grey rami. Thus while the grey rami link all the spinal nerves to the sympathetic chain the white rami link only a limited number.

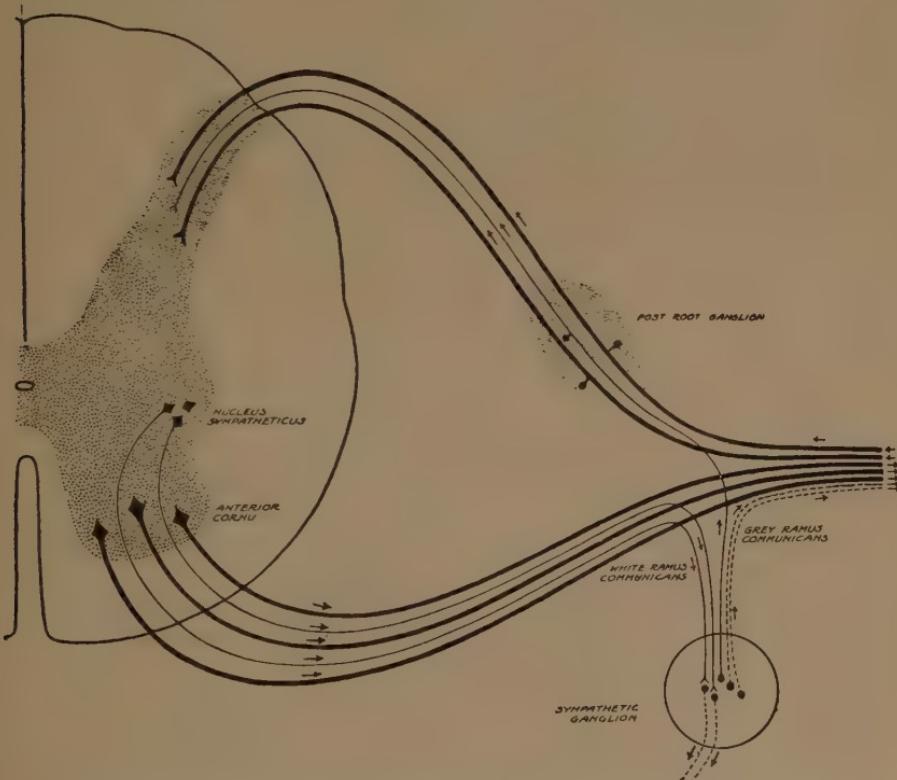


FIG. 176.—Diagram of the arrangement of Fibres in a Mixed Spinal Nerve (Purves-Stewart).

These connections have been proved by observing the results of stimulation of the various parts of the system, and in this way the paths for the various impulses have been discovered.

The cell stations have been discovered by the *nicotine method* of Langley and Dickinson, who made use of the fact that nicotine injected into an animal stimulates and then paralyzes synapses. If nicotine instead of being injected is painted on a sympathetic ganglion the synapses in that ganglion are paralyzed. Thus if stimulation of a portion of the sympathetic produces a certain

reaction and successive ganglia in the course of the distribution of the nerves are painted with nicotine it will be seen that the fibres pass through certain of the ganglia without ending in synapses. If nicotine is painted on the ganglion in which the synapses for any special reaction exist, that response will fail if the stimulation is central to the ganglion, but the response will be obtained if the stimulation is peripheral to it. By this method it has been proved that there is only one cell station in the path of each peripheral distribution.

The structures supplied from the sympathetic are widespread ; they include :—

The heart and blood-vessels.

The muscles and glands of the skin.

The muscles and glands of the alimentary canal.

The muscles and glands of the urogenital system.

The pupil and ciliary muscle of the eye.

The ductless glands.

To reach the peripheral blood-vessels and skin structures the grey rami carry the post-ganglionic fibres to the spinal nerves.

Passing in the cephalic direction from the upper thoracic nerves are pre-ganglionic fibres to carry impulses for all the parts above. The cervical ganglia are grouped to form the superior cervical ganglion, the inferior cervical and stellate ganglia. The cervical sympathetic is the nerve cord running from the inferior cervical to the superior cervical ganglia. It contains fibres for the upper four cervical nerves, the blood-vessels of the head, the pupil of the eye, the salivary glands, sweat glands and the muscles of the hairs (pilo-motor). Below the third lumbar nerve pre-ganglionic fibres run caudalwards to ganglia which in turn supply grey rami to the lumbar and sacral nerves.

Special pre-ganglionic fibres run through the sympathetic chain to reach peripheral ganglia ; these are the splanchnic nerves. Post-ganglionic fibres are given off as distinct nerves to the heart from the superior cervical, the inferior cervical and stellate ganglia. Stimulation of these nerves accelerates the heart.

The post-ganglionic fibres from the abdominal ganglia run to the various organs where they are usually related to a local nerve network of cells and fibres similar to the network found in such animals as medusæ.

**The Parasympathetic** consists of three parts, named according to the part of the central nervous system from which each arises. These are the tectal, bulbal and sacral divisions. Each consists of medullated pre-ganglionic fibres.

**The TECTAL DIVISION.** This consists of pre-ganglionic fibres in the third nerve which reach the ciliary muscle of the eye and the

circular muscle of the iris as post-ganglionic fibres. The cell station is in the ciliary ganglion, and the short ciliary nerves convey the fibres from the ganglion to the eye. Stimulation of this nerve causes constriction of the pupil and accommodation for near vision.

The BULBAR DIVISION consists of fibres (*a*) which pass out of the central nervous system in the seventh nerve and via the chorda tympani to the submaxillary and sublingual glands and (*b*) which form the vagus nerve to supply the heart, bronchi, stomach, liver, pancreas and intestine. In addition the ninth and eleventh nerves contain autonomic fibres.

The SACRAL DIVISION consists of fibres from the second and third sacral nerves to form the *nervi erigentes*. These fibres supply the colon, rectum, bladder and genital organs. The ganglia associated with the bulbo-sacral outflow are usually in the organs which are supplied by these nerves. They thus differ from the sympathetic system in which the ganglia are not situated peripherally.

The connections of both the sympathetic, tectal, bulbar and sacral divisions are shown in Fig. 177.

It is difficult to systematise the functions of all these various nerves, but in general the sympathetic nerves antagonize the tectal and bulbo-sacral nerves. The following brief statement gives the main points in connection with the various structures supplied by the autonomic nervous system.

*The Sweat Glands, Cutaneous Blood-vessels*, and other cutaneous structures have only a single supply which reaches them via the grey rami and the spinal nerves. Stimulation of these nerves causes constriction of blood-vessels, secretion of sweat and erection of hairs.

*The Eye* receives fibres from the third nerve and from the superior cervical ganglion. Stimulation of the former causes constriction of the pupil and of the latter dilation of the pupil. Cutting the nerves has the opposite effect. In addition to its action on the pupil the third nerve governs the process of accommodation.

*The Salivary Glands.* Stimulation of the chorda tympani causes a free flow of watery saliva from the submaxillary gland with dilation of blood-vessels whilst stimulation of the sympathetic supply causes the secretion of a small amount of thick viscid saliva and a constriction of blood-vessels. The two nerves together produce an augmented flow of saliva. The bulbar supply for the parotid gland is via the otic ganglion and the auriculo-temporal nerve.

*The Heart* receives fibres from the vagus, stimulation of which produces inhibition of the heart. This is of interest as it was the first nerve which was ever shown to have an inhibiting action

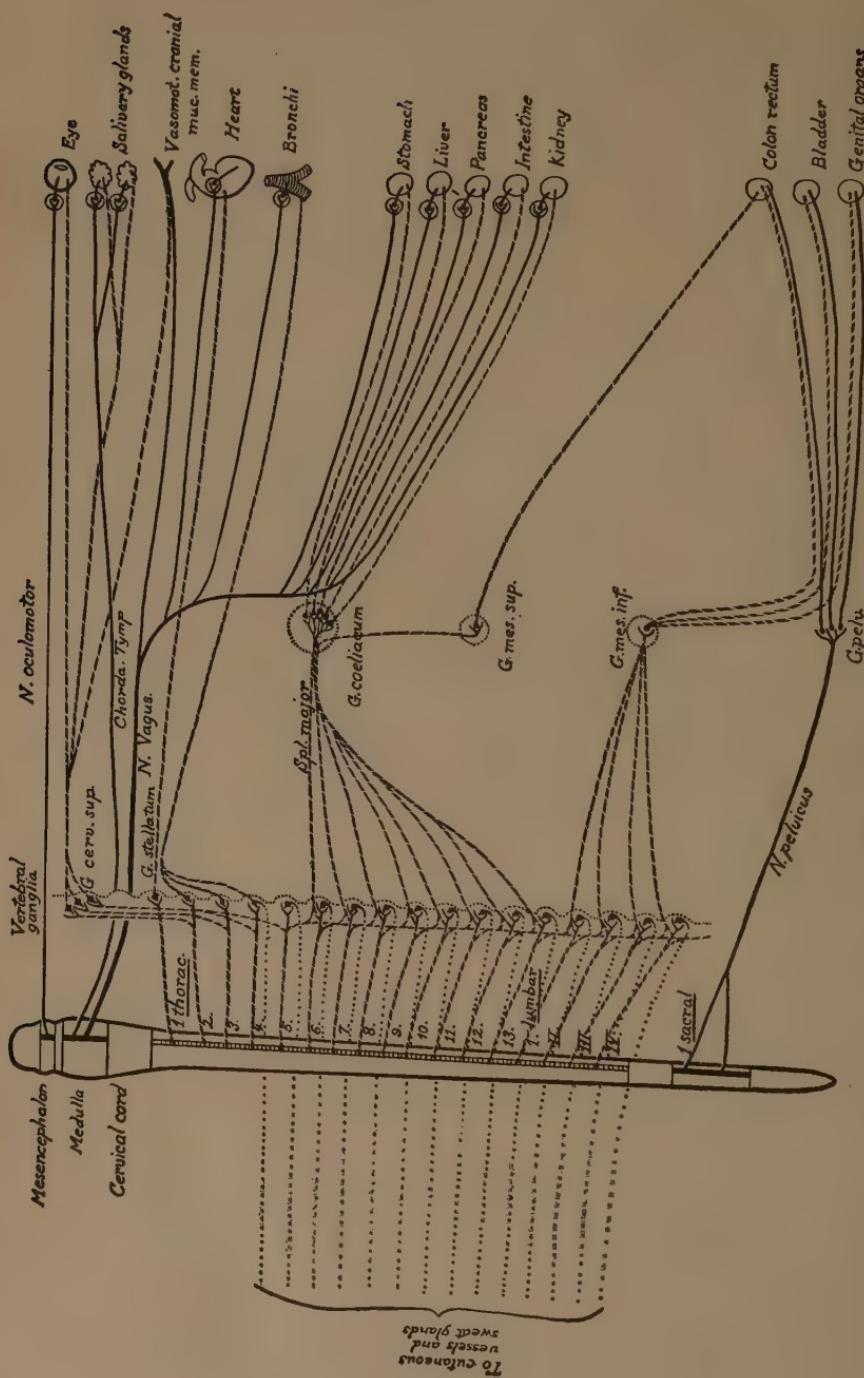


FIG. 177.—Diagram of the Autonomic Nervous System.

Solid black, the crano-sacral subdivision of the autonomic system; dash and stipple, the thoraci-columbar subdivision (modified from Meyer and Gottlieb).

(E. and E. H. Weber, 1845). Stimulation of the sympathetic fibres to the heart causes acceleration.

*The Bronchi* are controlled by both sympathetic and parasympathetic fibres and adrenalin causes relaxation of the muscles, being often used to relieve the spasm of the bronchi in asthma. The splanchnic nerves contain fibres for all the abdominal viscera, e.g. liver, kidneys, adrenals, etc.

*The Stomach and Small Intestine.* Through the superior mesenteric ganglion the sympathetic system supplies fibres stimulation of which causes inhibition of the intestinal movements and contraction of the sphincters (ileo-colic and perhaps pylorus). Stimulation of the vagus increases the movements of these portions of the alimentary canal, but it is not proved that relaxation of the sphincter muscles occurs at the same time.

*The Large Intestine and Rectum.* The inferior mesenteric ganglion is the cell station for the sympathetic supply. Stimulation of this supply causes inhibition of movements and contraction of sphincters (internal sphincter ani for example). Stimulation of the pelvic nerve causes increased rhythmical movements and relaxation of the sphincters.

*The Bladder.* Stimulation of the fibres from the inferior mesenteric ganglion causes contraction of the internal sphincter, whilst stimulation of the pelvic nerve causes contraction of the body of the organ and relaxation of the sphincter musculature.

*The Uterus.* This organ is supplied solely by the sympathetic system. Stimulation of the hypogastric nerves in virgin animals of some species causes relaxation of the uterus whilst in the pregnant condition contraction is the usual response (Dale).

*The Penis.* Stimulation of the pelvic nerve causes erection due to relaxation of the muscles of the blood-vessels and cavernous tissue; at the same time it causes relaxation of the retractor penis in those animals (e.g. dog) which have a retractor muscle. Stimulation of the sympathetic causes contraction of the retractor penis.

There is an interesting relationship between the action of certain drugs and the above divisions of the autonomic system.

*Adrenaline* generally produces the same effect as stimulation of the sympathetic. The coincidence is not complete since adrenalin does not stimulate the sweat glands.

*Ergotoxin* paralyzes the motor activities of the sympathetic. Thus after administration of ergotoxin, stimulation of the sympathetic or injection of adrenalin causes relaxation of the pregnant uterus.

*Acetyl-choline* has an effect corresponding to that of stimulation of the bulbo-sacral outflow.

*Pilocarpine* apparently stimulates the endings of the bulbo-sacral outflow, but in addition it causes secretion of sweat which is brought about by stimulation of the sympathetic system.

*Atropine*. Paralyzes the endings of the bulbo-sacral outflow.

*Nicotine*, stimulates and then paralyzes the synapses of nerves of the sympathetic system, and later it paralyzes the nerves to striated muscle also.

The details of innervation and of drug action on the autonomic system are rather complicated and for further information the student should consult W. H. Gaskell, *The Involuntary Nervous System*, 1916 (Longmans Green & Co.), and J. N. Langley, *The Autonomic Nervous System*, Part I, 1921 (Heffer & Sons).

## CHAPTER XXVIII

### SKIN SENSATIONS

We shall find later that afferent impulses can be divided into those which give us information about our surroundings, and those which regulate the bodily musculature.

The organs which are used for the former purpose are called extero-receptors, and they comprise those distance receptors such as the eye and ear, and the stimuli which originate by direct contact such as taste and skin sensations. The latter are brought about by "proprio-receptors" or organs which are stimulated by conditions inside the body. These must be described in relation to the regulation of bodily movements. In addition there are receptors known as "entero-receptors" which are stimulated by conditions in the alimentary tract and viscera.

All our knowledge of our surroundings is obtained by means of sensory organs. These consist essentially of end organs for the conversion of physical and chemical changes into nerve impulses, although in some cases, e.g. pain, the nerve impulse originates in what are apparently naked nerve fibres.

In the skin the nerve fibres run in the dermis and most of the endings are in the papillæ, but some fibres end as naked fibres amongst the cells of the epidermis and others end round hairs, etc. (See Fig. 272 for the structure of skin.)

Analysis of cutaneous sensibility shows that it consists of the ability to distinguish touch, pressure, pain and differences of temperature. The last can be shown to consist of the power to distinguish between temperatures warmer and colder than that of the skin. Methods for the investigation of sense organs depend in general upon presenting unusual forms of stimuli so that an analysis of the results will give us some information about the way in which the sense organs carry out their functions. With normal stimuli the sense organs are attuned to give us information about the stimulus whilst the mode of action of the sense organs themselves is concealed. One of these methods is to use stimuli which can be confined to a minute area of the skin, and which can be measured in physical units.

After cutting a cutaneous nerve the end organs supplied by that nerve will not be able to affect the nervous system so that the area

of skin to which that nerve was distributed will be rendered insensitive. Nevertheless under these conditions pressure on the denervated area can be appreciated ; the stimulus of pressure therefore must affect end organs supplied by nerves which run in structures below the skin. We shall return to this subject after we have dealt with the sensations in the skin itself.

The various types of endings in the skin are shown in Figs. 178-183.

Touch sensations are believed to be associated

FIG. 178.—End Bulb of the Human Conjunctiva (Krause).

with Krause's end bulbs (Fig. 178), and Meissner's corpuscles (Fig. 182).

*Krause's end bulbs* are bulb-like structures covered by a capsule.

Inside the capsule are a series of ovoid cells amongst which the endings of a medullated nerve ramify.

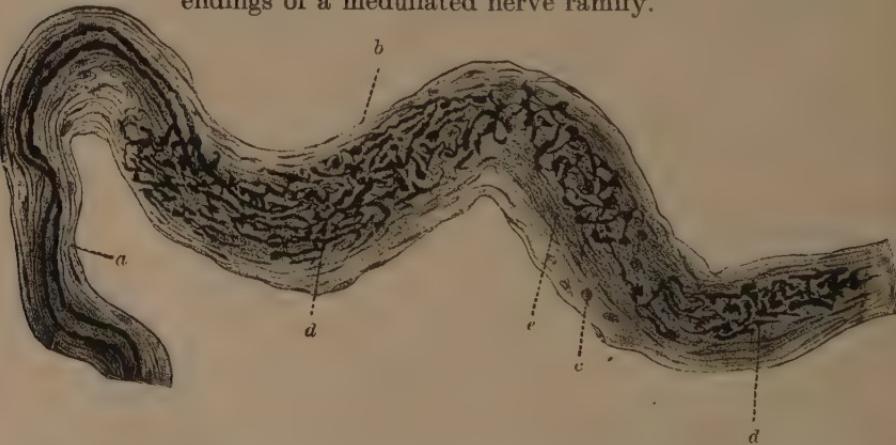


FIG. 178.—End Bulb of the Human Conjunctiva (Krause).



FIG. 179.—Pacinian Corpuscle (Flack and Hill).

*a* = sheath of entering nerve, *b* = sheath of terminal organ, *c* = blood capillaries, *d*, *d* = terminations of axons, *e* = spindle-shaped connective tissue core in which these terminations ramify.

*a* = sheath of entering nerve, *b* = sheath of terminal organ, *c* = blood capillaries, *d*, *d* = terminations of axons, *e* = spindle-shaped connective tissue core in which these terminations ramify.

Pressure is probably received by end organs known as *Pacinian corpuscles* (Fig. 179), which are laminated structures somewhat like an onion in appear-

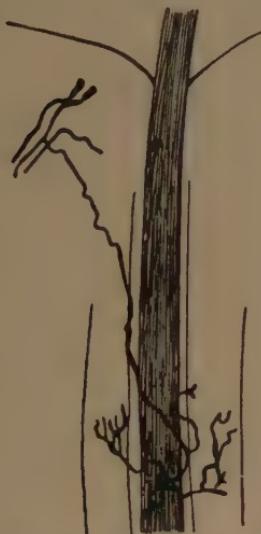


FIG. 181.—Showing Sensory Nerve Endings at the Base of a Hair (redrawn after von Gehuchten from Dahlgren and Kepner).

ance. A naked axon from a medullated nerve forms the core of each corpuscle.

*Ruffini's* (Fig. 180) endings in connective tissue may also be a receptor for touch sensations.

Nerve endings round hairs may be responsible for the delicate sense of touch produced by moving a hair (Fig. 181).

*Meissner's Corpuscles* (Fig. 182) are another type of encapsulated ending. They are elongated structures within each of which a medullated nerve fibre ends.

Naked nerve endings in the epidermis are probably responsible for the sensations of pain (Fig. 183).



FIG. 182.—Meissner's Tactile Corpuscle. Methylene-blue Stain (Dogiel, Böhm-Davidoff Huber).

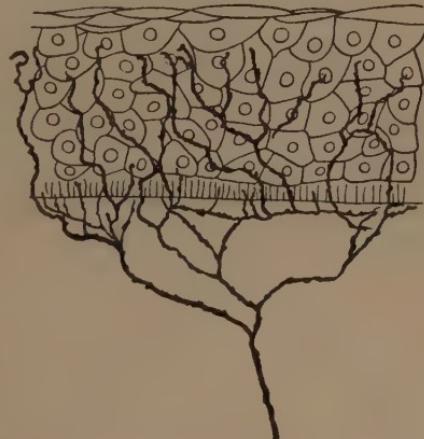


FIG. 183.—Sensory Nerve End-organ in External Epithelium of Pig's Snout.

**Sensations of Temperature.** By using a metallic object with a rounded end, i.e. one which will touch only a small area of the skin but is not sharp, it is possible to examine the skin for the temperature sense. If the object used is hollow it can be kept at a constant temperature by a stream of water, or if solid a hole may be drilled in it into which a thermometer can be inserted.

A simple means of investigation is to use large (six-inch) wire nails with rounded points. If such a nail is cooled by means of ice, then dried and moved slowly and gently in parallel lines over a definite area of skin a sensation of cold will be felt at certain spots which can be marked by coloured ink. This shows the first important fact, namely that the sense organs are punctiform in distribution, which agrees with the observation that most nerve fibres end in definite end organs.

If now a similar nail is warmed to about  $40^{\circ}$  C. and the same area of skin is examined we can mark the spots where hot sensations can be aroused. It is found that the hot and cold spots are not at the same but at different points on the skin and that the cold spots are more numerous than the hot. The

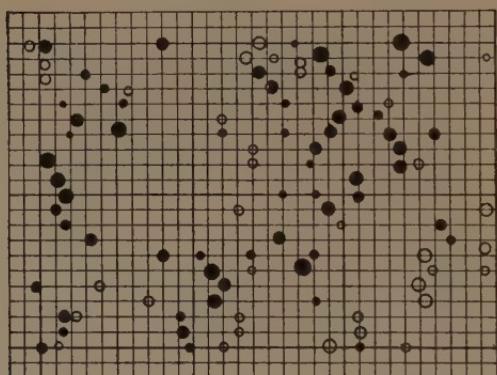


FIG. 184.—Heat and Cold Spots (somewhat enlarged; after Donaldson, from Halliburton's *Handbook of Physiology*, John Murray).

The diagram shows the distribution of heat and cold spots over six squares, each 1 sq. cm., on the back of the hand. ● = cold spots, ○ = hot spots. The sizes suggest the strength of the reaction.

various spots are frequently arranged in groups or linear series and this arrangement suggests that a group of endings correspond to the branching of a single nerve fibre to form several endings such as is seen in histological preparations of a nerve fibre near its termination.

Further if a cold spot be selected which gives a well marked response, and if it be touched by a hot rod about  $45^{\circ}$ - $50^{\circ}$  C. a cold sensation is produced; this is called a *paradoxical cold sensation*.

Electrical stimulation of the various spots produces the sensations characteristic of those spots.

From these observations we see that the sensation produced does not depend upon the nature of the stimulus but on the end organ stimulated.

The normal stimulus, i.e. hot object on a hot spot, is called the adequate stimulus, whilst other forms of stimuli are known as inadequate stimuli.

There is one factor in sensation, that of contrast, which makes sensation different from a physical measurement. For example, if one hand is put in water at 15° C. and the other in water at 35° C. for some minutes, and then both hands plunged into a vessel of water at 25° C. the hand which had been in cold water feels warm, and that which had been in warm water feels cool. This effect of contrast should be thought of in connection with the fact that nerve is stimulated by change of current and not by strength only. It is a striking circumstance that the human mind has worked out methods of absolute measurement to supplement the relative measurements of the senses, and that only where sensation must be relied upon do we lack such absolute measurements. We can make, for instance, absolute measurements of the heating or chemical effect of light, but we can only compare the illuminating power of two lights. We shall find this contrast effect in all sensory systems.

**Uniformity or Diversity of Nerve Impulses.** At this stage it is necessary to discuss the relation of sensations to nerve impulses.

Every sensation gives information of three distinguishing features, namely quality, intensity, and space-position.

*Quality* is a property by which one kind of sensation differs from another. It depends upon the physical nature of the stimulus which normally produces it. Thus light excites the eye, sound the ear, etc. Further in the case of some senses we can distinguish subqualities, such as colour in vision, tone in hearing, and we may group the various sensations arising from the skin as subqualities of cutaneous sensibility.

*Intensity* denotes the apparent strength of the sensation, and it must be correlated to the magnitude of the exciting cause.

*Space-position* depends upon the situation which is stimulated, but we generally refer the stimulus to the object which produces the stimulating agent, e.g. the source of a light.

*Succession in time*, if we add this factor, forms a fourth feature by which we distinguish one sensation from another.

Of these the last does not need further discussion as one sensation which is felt after another is said to be later in time, but we must attempt to explain how nerves can convey the other sensory properties to the brain.

The discussion of this subject hinges upon whether a single nerve fibre can convey more than one type of impulse or whether a nerve impulse is always of the same nature. If the former is the condition of affairs there is no need for a peripheral analyzing organ, but merely a mechanism which converts the stimulus into

a nerve impulse and the analysis of the sensation must be carried out by some unknown central organ:

If the latter is true, namely that a nerve impulse is always of the same nature, then the analysis is the work of the peripheral organs and the sensation produced is the result of the anatomical arrangements, i.e. of the situation in the central nervous system at which the impulse ultimately arrives. Thus if it were possible to shunt an impulse travelling in the optic nerve into the paths along which an impulse would travel from the cochlea, instead of a visual sensation being produced a sound would be heard. An extension of this discussion leads us to consider whether it is necessary to have different nerve fibres for different colours or for different tones or whether the different colours or tones can travel up one and the same nerve fibre and be separated in the brain.

Although it is always possible to take refuge in the assumption that one nerve fibre can convey several forms of impulse, and the analysis be carried out by some hitherto undiscovered organ in the brain this is at present merely a confession of failure or a form of mental laziness. We ought to attempt some explanation with our known facts as such attempts may lead to further facts which may ultimately indicate the true explanation. All the known facts suggest that a nerve fibre can convey only one form of impulse and not several.

In the case of the different senses of vision, hearing, taste, smell and cutaneous sensibility we have anatomical evidence that the sensations are sorted, and ultimately reach different areas of the cortex as we saw in studying cerebral localization.

If we regard the various sensations from the skin as analogous to different colours and tones we find that there is a sorting into tracts in the spinal cord. Thus a mixed spinal nerve may convey impulses for heat, cold, touch, pain and pressure, and we find that in the spinal cord these impulses travel by paths so that heat, cold and pain are conveyed by the lateral spino-thalamic tracts whilst touch is conveyed by the ventral spino-thalamic and spino-bulbar tracts. Further lesions of the grey matter of the spinal cord such as spina bifida (Syringomyelia) causes dissociation of sensations. The grey matter is pressed upon by overgrowth of neuroglia. Cold, heat and pain sensations are interfered with before those of touch.

In all cases we find evidence of analysis by peripheral structures, although in the eye the evidence is less complete than in the case of the other sensory organs. This evidence of analysis is not of fundamental importance but it shows that sensations can be sorted peripherally and that if they are mixed again in order to pass up the same nerve fibres, then a second analytical structure is required

which is redundant on the supposition that only one type of nerve impulse can pass up a single nerve fibre. The evidence for analysis will be discussed later under the headings of the various senses, but we have already had one good example in the case of the hot and cold sensations. In support of the view that several different kinds of impulses can travel along the same nerve the analogy is often quoted that it is possible to send several electrical impulses along the same wire. The conditions of such electrical transmission must be borne in mind. The principle is that receiving instruments must be devised to detect the different forms of electrical impulses, and if such analogy is to receive support some analytical mechanism should be sought in the brain. Without such evidence the analogy is of no value.

The analytical mechanism for electrical impulses must be tuned, as in tuning a receiver for wireless waves. It may be that the dendrons of nerve cells may be tuning mechanisms but no proof of such action is yet known.

If we regard the nerve impulse as a wave passing along the nerve we see that such a wave may vary in amplitude, in frequency and possibly in form, and these are factors which may be capable of analysis by some form of analyzer. We may or may not be justified in identifying the nerve impulse with the electrical change in a nerve, but this change is the only physical counterpart which has been discovered which can be identified with the nerve impulse.

Taking first the amplitude of the nerve impulse we have the evidence of experiments by Adrian on conduction through a region where the impulse is gradually extinguished (see p. 301). If the impulse does pass through such a region it recovers its former magnitude, and therefore the amplitude seems to be a function of the local condition of the nerve and cannot be utilized to differentiate one form of nerve impulse from another.

The frequency with which impulses can follow each other up a nerve is limited by the latent period of the nerve. Thus Keith Lucas found that a second electrical stimulus produced no effect when sent into a nerve within  $2\sigma$  after the first which limits the frequency to 500 a second. Different nerves may have different frequencies, but one cannot imagine that frequencies of sound up to 30,000 per second, much less those of light, can be attained. There remains the supposition that each nerve impulse may consist of a series of rapid oscillations but such a view is a mere speculation and is inconsistent with the diphasic character of the electrical variation in a nerve.

It is unlikely that the form of the wave will vary from that of a sine curve. It might be unsymmetrical with a steep rise and slow fall or slow rise and steep fall, but such variations would not be

likely to produce the smooth electrical potential curves found with the nerve impulse.

Thus, to account for the properties of quality and intensity of a sensation we have merely variations in frequency up to a rate of 500 per second. The locality of a sensation is so obviously anatomical that it need not be considered in this discussion.

For reasons to be given later it seems best to reserve the frequency with which impulses reach the nervous system for variation in intensity of the sensation so that the quality of the sensation is left to be dealt with by different nerve fibres.

Of course it is possible to prefer some hypothesis without any foundation, but we have considered those that seem at all feasible and have given reasons why some of them seem to us improbable.

If we look upon the various qualities and sub-qualities as being conveyed by different nerve fibres we must attempt to show how physical stimuli can be sorted so as to produce impulses in different nerves. In the case of hot and cold sensations we found that there were separate end organs for each sensation and that they were grouped as if one nerve fibre supplied a group of cold spots or a group of hot spots. If, however, it can be proved that one nerve fibre supplies both hot and cold spots then the views advanced here must be modified. Once we can sort impulses as just described then the rest of the reception is easier to understand as the sensation evoked will depend on the nerve cell or cells in the cerebrum at which the impulse ultimately arrives.

### Touch Sensations

The sensations of touch can be investigated by graduated pressures and the term touch is confined to light pressure only; heavy pressure affects sensory organs below the skin and gives rise to a different sub-quality known as pressure.

Light pressure is best investigated by hairs or bristles attached to a holder (von Frey). The pressure can be standardized by pressing the hair against the scalepan of a balance, and noting the weight that it can balance without bending. By measuring the sectional area of the hair the pressure per unit of surface can be determined. The acuity of touch for different parts of the body is shown in Table XLVI on opposite page.

The end organs for touch are said to be Meissner's corpuscles, but growing hairs also serve as sensory organs. By touching the tip of a stiff hair a touch sensation is produced. In fact the hairs act as small levers so that pressure on their outer ends moves the part embedded in the skin. The shaft of the hair is surrounded by a nerve network which is presumably also an ending for touch sensations.

TABLE XLVI

## ACUITY OF TOUCH SENSATIONS (MYERS)

*Region.*

| <i>Region.</i>                     | <i>Pressure.</i>   |
|------------------------------------|--|
|                                    | In gms. per sq. mm.  |
|                                    | Area of Contact—<br>$\frac{1}{300} - \frac{1}{10}$ sq. mm. |
| Tongue and Nose . . . . .          | . . . . . 2  |
| Lips . . . . .                     | . . . . . 2.5  |
| Finger Tip and Forehead . . . . .  | . . . . . 3  |
| Dorsal Surface of Finger . . . . . | . . . . . 5  |
| Palm, Arm and Thigh . . . . .      | . . . . . 7  |
| Skin and Sole of Foot . . . . .    | . . . . . 28   |
| Loins . . . . .                    | . . . . . 48   |

The sense of touch is due to deformation of the skin as shown by the familiar experiment of dipping a finger into a cylinder of mercury. In order to get rid of temperature sensations which interfere with the purely tactile sensation the mercury should be at the temperature of the skin. The sensation is that of a ring round the finger at the level of the surface of the mercury, because below the surface the skin is pressed on evenly, but at the surface the skin is formed into a ridge.

**Pain Sensations.** Any cutaneous stimulus if of sufficient severity may produce the sensation of pain, but the penetration of the skin by a sharp instrument is the most effective method of stimulation. A needle can be used, and if one wishes to measure the force necessary to produce the sensation the needle may be backed by a hair or bristle, the pressure exerted having been standardized by a balance as described previously.

This distinct pain-sensation is believed to be received by naked nerve endings which are widely distributed between the epithelial cells of the epidermis.

The physico-chemical mechanisms by which the stimuli can be converted into nerve impulses cannot yet be described, so one must resort to analogy. For example, pressure can give rise to electrical changes or cause a change in chemical equilibrium. If a chemical or physical change is accompanied by an increase in volume it is known that an increase in pressure promotes the reverse change, i.e. that in which decrease in volume will occur. The rate at which the change occurs will depend upon the increase in pressure, and as most chemical changes are accompanied by electrical changes an increase in pressure might stimulate a nerve ending through the electrical effect.

In the case of temperature sensations if we assume that the stimulation of the nerve is due to either acid or alkali we can give a chemical analogy to the two separate hot and cold sensations. Let us for example choose acidity as the nerve excitant. If one dissolves excess of aniline in hydrochloric acid and uses the clear

solution of aniline hydrochloride to which an indicator has been added it will be found that warming the solution makes it more acid : hence an increase in temperature would produce a stimulation. If on the other hand one adds phenolphthalein to a solution of sodium acetate it is found that warming the solution causes it to become alkaline, which is equivalent to cooling, producing acidity. Thus by a combination of a weak base with a strong acid and a strong base with a weak acid the two different temperature changes produce the same chemical change, namely increase of acidity. It may be that special proteins play the parts of weak base and weak acid respectively.

The amount of chemical change will depend on the physical cause of the change, but this continuous effect must be transformed into interrupted nerve impulses. It is not difficult to find an analogy to this conversion of a continuous into an interrupted activity. A globule of mercury in an oxidizing solution shows pulsation due to periodic removal of the skin of mercury oxide. The rate of pulsation depends on the concentration of oxidizing substances ; one sees, therefore, how it is possible to relate strength of physical stimulus to the number of nerve impulses produced in a given time.

Granted the hypothesis that the strength of a sensation depends on the number of impulses that reach the interpreting area of the cerebrum one can then explain a further peculiarity of sensations, namely *extensity*. This term is used to denote the fact that the area of an object affects the sensation produced by it : the larger the area of surface stimulated the more intense the sensation. Thus the larger of two pieces of the same metal raised to the same temperature appears the hotter. Presuming that the sensation produced depends upon the number of nerve impulses that reach the nervous system we can understand that the warmer of two objects feels hotter because it produces a more rapid succession of impulses in the same fibres, whilst a larger object seems warmer than a smaller one because although the frequency of stimuli up each nerve is the same the total number of nerves involved is larger, hence more impulses impinge upon the nervous system in the same time.

In the preceding paragraphs we saw that localized end organs can be stimulated by localized stimuli, but for some purposes it is desirable to use stimuli by which it is possible to explore larger areas more quickly. For such purposes test tubes containing hot or cold water can be rolled over the skin to see if the skin is sensitive to these stimuli. For touch sensations a camel-hair brush, a pledget of cotton wool, or the subject's own finger may be used to map out areas insensitive to touch.

We may further test the accuracy of an individual in localizing the place of application of the stimulus. With the part to be tested screened from view one may ask the subject to indicate the part stimulated, either by describing it or by touching it with a finger, or by touching the corresponding part of some person whom the subject can see. The last method is probably best, and the distance between the point corresponding to the area stimulated and the point indicated is a measure of the accuracy of localization.

The localization of sensation is obviously related to the anatomical distribution of nerves, so that stimulation of a single nerve fibre should be referred to the area of skin to which that fibre is distributed. Such a supposition has much to recommend it, and as it is the simplest possible conception it may be accepted for the present.

If two points of skin close together are stimulated simultaneously one may obtain the sensation of two points being touched, or of only one, depending on the distance apart of the two spots touched. This power of spatial discrimination varies for different regions of the body.

Table XLVII shows the average distances apart at which two simultaneous stimuli can be felt as two distinct sensations when the subject is prevented from seeing the part stimulated. If individual touch spots are marked and stimulated the interval between them required to produce a sensation of two points is less than if the surface is touched at random.

TABLE XLVII  
SPATIAL DISCRIMINATION (MYERS)

| <i>Region.</i>                           | <i>Distance of the Points.</i> |
|--|--------------------------------|
| Tip of Tongue . . . . .                  | . 0·1 cms.                     |
| Tip of Finger (palmar surface) . . . . . | . 0·2 „                        |
| Lips (outer surface) . . . . .           | . 0·3 „                        |
| Tip of Nose . . . . .                    | . 0·7 „                        |
| Tip of Finger (dorsal surface) . . . . . | . 0·7 „                        |
| Lips (inner surface) . . . . .           | . 2·0 „                        |
| Back of Hand . . . . .                   | . 3·2 „                        |
| Forearm, leg and sacrum . . . . .        | . 4·0 „                        |
| Arm and Thigh . . . . .                  | . 6·8 „                        |

The power of discrimination is greatly increased by practice, and is best developed in those parts which habitually distinguish small differences. Thus a small hole in a tooth is always felt as a large one by the tongue because it is able to distinguish small distances which are mentally compared to the larger distances required to produce separate sensations elsewhere. Localization and discrimination are markedly affected by fatigue, temperature of skin, etc., thus showing how difficult it is to give a simple explanation of the mechanism of discrimination.

Although there is a large psychological factor concerned, the following diagram (Fig. 185) may help to explain some of the factors concerned. The consideration of the problem is necessary as it recurs in other sensory organs.

If three separate nerve fibres, A, B and C, are represented, breaking up into a series of nerve endings, one sees that opposite B there is an area a stimulus to which will stimulate fibre B alone, if the stimulus is weak, but a strong stimulus will affect A and C as well, thus explaining the greater effect of spread of sensation with a stronger stimulus.

A weak stimulus moved towards the right from B will produce impulses in B and C until it reaches the area opposite C, where C alone may be affected. As one moves the stimulus along, the relative number of stimuli up B and C will vary because of the varying number of end organs from B and C stimulated. Moving the stimulus to the left will cause a similar mixture of impulses up

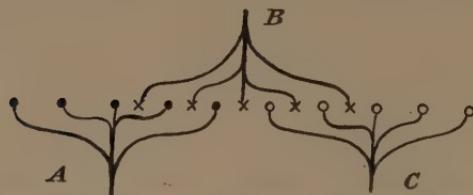


FIG. 185.—Diagram to show how Nerve Endings from different Nerve-Fibres may Overlap.

The endings of nerve fibre A are represented by dots, those of B by crosses, and those of C by rings.

A and B until the stimulus is opposite A. Thus to feel two stimuli as separate they must be sufficiently far apart to give very few or no impulses up B, but well definable impulses up A and C or fibres at least as far apart as these two.

In an actual sensory area the distribution of the end organs will not be so simple and one must remember that an area has two dimensions, so that there is the possibility of the distribution of three or four nerve fibres overlapping.

In such a complicated system it is easy to understand how fatigue may diminish the accuracy with which the nerve cells in the cerebrum can differentiate the actual number of impulses coming from the neighbouring areas supplied by a group of nerve fibres.

In the investigation of cutaneous sensations nerve injuries furnish a certain amount of information, but more accurate results were obtained when Head, Rivers and Sherren cut individual cutaneous nerves and followed the changes in sensation whilst the nerve fibres were regenerating.

The cutaneous nerve may be localized by stimulation with a weak faradic current, the large electrode being placed on some other region of the body. A fluttering sensation is experienced in the area of distribution of the nerve when the pointed stimulating

electrode is just superficial to its trunk (Trotter and Davies). The skin is marked indelibly, so that the nerve is easily found by a small operation wound through the mark. At the operation the nerve is cut and sutured, so that the processes of regeneration may be studied as well as the effect of interruption to the passage of impulses.

The immediate effect of the operation is loss of sensation in the area supplied solely by the nerve that has been cut. There is complete loss of the sensations of superficial pressure (touch), cold, heat and superficial pain, but sensations of deep pressure and deep pain produced by heavy pressure still persist, thus showing that pressure sensation is dependent on structures innervated by deep nerves. There is also a loss of vaso-motor, pilo-motor and sudomotor influences in the denervated area.

Regeneration of the nerve is sometimes sufficiently advanced to give some return of sensation by the tenth week, but before this time there may be local areas of hyperalgesia associated with superficial veins. Before recovery occurs the denervated area is unnoticed, but between the tenth and fourteenth weeks sensation to touch commences to return, and it, as well as other sensations, are frequently referred to the most peripheral part of the denervated area. With returning sensation it is found that many abnormalities exist, the principal ones being decreased sensitivity to touch, with an increased sensitivity to pain. The decreased sensitivity to touch is accompanied by a raised threshold, that is a stronger physical stimulus is required to evoke sensation. Warm and cold sensations are evoked only by temperatures further removed from the normal skin temperatures than usual. The temperature sense is normally due to rate of gain or loss of heat, and not by a definite temperature applied.

The fact that temperature sensations are caused only by extremes of temperature caused Head to describe two types of sensation : (1) protopathic, for pain touch and for differences of temperature below  $26^{\circ}$  and above  $37^{\circ}$  C. ; and (2) epicritic, for localization and discrimination of touch and for temperatures within the range of  $26^{\circ}$  and  $37^{\circ}$  C.

Trotter and Davies point out that one must distinguish between the threshold at which a sensation is produced and the intensity of the resulting sensation. They claim that many of the abnormalities observed during recovery of sensation may be produced by an excessive pain factor in sensation. The explanation of the phenomena of recovery of sensation can best be explained by the following considerations.

When a nerve is cut the peripheral portion degenerates, but we do not know what changes may occur in the end organ. Perhaps like muscle the nerve ending may undergo degenerative changes. When the nerve regenerates it is possible that axons may grow

into sheaths which belonged to other axons. This is known to occur with efferent nerves to muscles, but we do not know whether an afferent nerve for touch impulses grows into a path leading to a touch ending or whether it may grow into a path leading to a cold or warm end organ.

Therefore when an axon re-establishes connection with an end organ it may be some time before the contact is perfected, as it may be necessary for the end organ to recover from a certain amount of degeneration. Thus one might expect to find that a stronger stimulus is required to initiate a nerve impulse, i.e. the threshold is raised.

Further, if a touch fibre grows into an end organ for cold sensations it may take longer for the end organ to become adapted to the nerve fibre, so that the physical stimulus can be passed on to the fibre as a nerve impulse. Stimulation of this touch organ should produce a cool sensation if the anatomical considerations in the early part of this chapter are correct. In order that a normal relation between stimulus and sensation may be established the part must be re-educated so that the nerve impulses reaching the central nervous system can be interpreted. This process of re-education will require time, just as the original process of education for the interpretation of sensations in a child requires time. That such a process of re-education is possible is shown in the case of vision. When glasses which invert images are worn for some time the eye becomes re-educated to interpret objects in their proper position; this fact is familiar to any one who is accustomed to focussing objects on the ground-glass screen of a camera.

Although these hypotheses require verification there is sufficient latitude of interpretation to allow for the phenomena of regeneration. The recovery process can be sufficiently explained by the adaptation of the axon to the end organ, the re-tuning of the end organ and the re-education of the central connections of those nerve fibres which have become linked to different sorts of end organs from those to which they were originally connected, so that it is not necessary to imagine different sorts of fibres, such as protopathic and epicritic. The delay in the ability to localize touch sensations and to discriminate two simultaneous touch sensations is particularly suggestive of a process of re-education.

The cutaneous sensations pass into the spinal cord by the dorsal root. In the cord they end partly in cells in the dorsal grey column, whence they are relayed to the ventral and lateral spino-thalamic tracts and partly in the nuclei gracilis and cuneatus by fibres which pass up in the dorsal columns (see Fig. 174).

## CHAPTER XXIX

### TASTE AND SMELL

The skin being impervious to liquids does not contain receptors for chemical stimuli. Corrosive liquids may destroy the skin and produce pain, but they do not cause any sensation of a chemical nature. Receptors in the mouth, pharynx and nose are adapted for the chemical stimuli associated with taste and smell.

#### Sense of Taste

The mucous membrane on the sides and dorsum of the tongue is not smooth like the epithelium of the skin but is raised to form a rough surface which can be felt. This is especially marked in such animals as a cat or a dog. The papillæ of the skin are projections of the dermis over which the epithelium is moulded to form a smooth surface, whilst in the tongue the papillæ raise the epidermis to form projections on the surface. The papillæ of the tongue consist of three varieties.

(a) Conical Papillæ (see Fig.

68). These consist of thin tapering papillæ which are sometimes subdivided into a number of thinner strands, when they are called filiform papillæ. The conical papillæ are found all over the upper surface of the tongue.

(b) Fungiform Papillæ are squat rounded forms which resemble

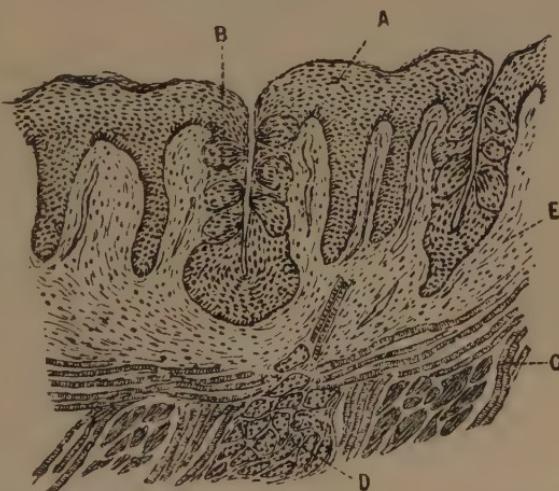


FIG. 186.—Microscopic View of a Section through a Circumvallate Papilla (Leonard Hill).

A = epithelium, B = taste buds, C = muscle, D = glands, E = sub-epithelial layer.

"puff ball" fungi. They are found chiefly at the sides and tip of the tongue.

(c) *Circumvallate Papillæ* are large cylindrical structures, but owing to the fact that they arise from a depression they do not project much above the general level of the tongue. The wall of the depression with the side of the papilla form a narrow trench round the papilla to which its name is due. These papillæ in man are found in a V-shaped area the apex of which is at the foramen cæcum and the two limbs extend forwards and outwards.

In some animals, e.g. rabbit, the circumvallate papillæ are replaced by a series of ridges on each side of the back of the tongue, known as the papillæ foliatæ.

*Taste Buds.* In the sides of the moats surrounding the circum-

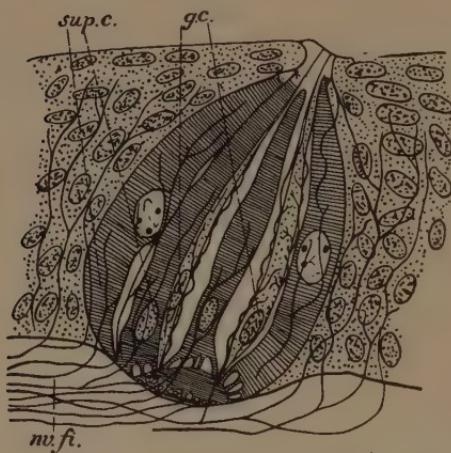


FIG. 187.—Taste Bud in Human Tongue (Flack and Hill, redrawn after Hermann from Dahlgren and Kepner).

whether there are other receptors which can also interpret chemical stimuli due to non-volatile substances.

The taste sensations are tested by the use of solutions of non-volatile substances. Volatile substances cause complicated reactions owing to their passage by the anterior or posterior nares to the endings for smell. The tongue is protruded, dried with a piece of soft cloth in order to limit the spread of liquid when it is applied to the tongue. A small pointed camel-hair brush is moistened with the liquid to be tested and the tip of the brush is applied to the tongue. If the drop that is applied is not so large that it spreads over the surface of the tongue a localized stimulus will result. By such stimuli it has been found that there are four distinct kinds of taste sensations, namely sweet, acid, salt and bitter.

vallate papillæ are found small oval structures known as taste buds. These consist of a capsule containing closely packed fusiform cells. Stiff hair-like projections of the fusiform cells extend through a pore at the free pole of the taste bud. Nerve fibres ramify amongst the fusiform cells.

The taste buds are found also on the palate, pharynx, cheeks, epiglottis and on some of the fungiform papillæ. They are regarded as the end organs for taste, but we do not know

The receptors for sweet sensations are most numerous on the tip and dorsum of the tongue. Acid is recognized on the dorsum save for a small area near the tip of the tongue. Salt causes its special sensation when applied to the dorsum except for a small area just behind that insensitive to acid. Bitter is best recognized at the sides and back of the tongue. The sensitivity of the endings for taste is shown in Table XLVIII, where the minimum concentration which can be tasted is given.

TABLE XLVIII  
ACUITY OF TASTE SENSATIONS (VALENTIN)

| Substance.                | Content.<br>Percentage. | Amount of<br>Solution.<br>c.c. | Absolute amount<br>of Substance. |
|---------------------------|-------------------------|--------------------------------|----------------------------------|
| Sugar . . . . .           | 1·2                     | 20                             | 0·240                            |
| Sodium chloride : . . . . | 0·4                     | 1·5                            | 0·007                            |
| Sulphuric acid . . . .    | 0·2                     | 12                             | 0·027                            |
| Quinine sulphate . . . .  | 0·003                   |                                | marked                           |
|                           | 0·0001                  |                                | barely recognizable.             |

It is possible to paralyze one form of taste sensation before another. Cocaine and the leaves of *Gymnema Sylvestre* (*gymnenic acid*) abolish the sensations of sweet and of bitter before those of acid and of salt. The taste sensations are additional to those of touch, temperature and pain which have been described in relation to the skin sensations. The sensitivity of the tongue to touch is very great, as can be seen from Tables XLVI and XLVII. The central connections for taste are shown in Fig. 188. They all reach the

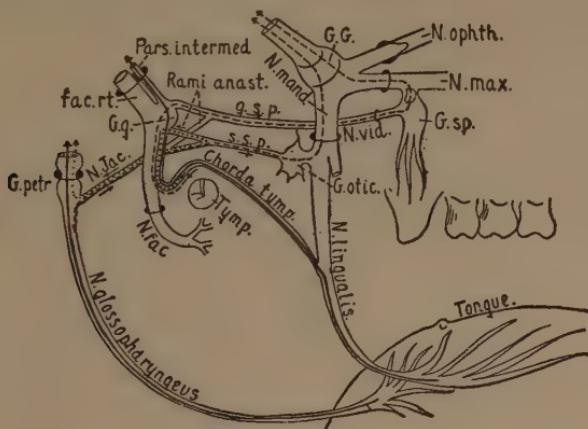


FIG. 188.—Diagram of the Trigeminal, Facial, and Glosso-pharyngeal Nerves showing the Course of the Taste Fibres in Solid Black Lines.

*a* = sheath of entering nerve, *b* = sheath of terminal organ, *c* = blood capillaries, *d*, *d* = terminations of axons, *e* = spindle-shaped connective tissue core in which these terminations ramify.

The broken and dotted lines indicate the course which according to certain investigators some of the taste fibres are supposed to take: *G. g.*, Gasserian ganglion; *G. gen.*, geniculate ganglion; *G. sp.*, sphenopalatine ganglion; *g.s.p.*, great superficial petrosal nerve; *N. Jac.*, the tympanic nerve of Jacobson; *N. vid.*, vidian nerve; *s.s.p.*, small superficial petrosal nerve (Cushing).

tractus solitarius whence they pass to the optic thalamus and to the cortex.

### Sense of Smell

In aquatic animals taste and smell are a single chemical sense, but in land animals the two senses are differentiated, namely those due to direct contact with the substance and those which are appreciated at a distance. This difference is due to a difference in volatility. Taste is therefore due to substances which are not necessarily volatile, whilst smell is due to volatile substances. Such a distinction is not absolute ; chloroform, for instance, has a sweet taste as well as a smell, and the sweet taste will be noticed if sufficient chloroform reaches the tongue, even if it arrives in the form of a vapour. Most flavours are a combination of taste and smell, the smell element passing to the nose round the soft palate to the posterior nares.

The sensory area is confined in man to about 250 sq. mm. on the upper wall above the superior turbinated bone and on the upper part of the septum. When we wish to sample an odour we sniff in order to project the air current against the upper part of the nasal mucous membrane.

Fig. 189 shows the typical structure of the sensory epithelium which contains special ciliated cells, with which the olfactory nerve fibres connect.

It is not possible to sort the substances which stimulate the sense of smell into a few groups but the following list is given in order to show the kind of classification which has been attempted.

TABLE XLIX

CLASSIFICATION OF VARIOUS KINDS OF SMELLS (LINNE)

1. Aromatic odours, such as turpentine, peppermint and lavender.
2. Fragrant odours, such as those of the lily, jasmine and vanilla.
3. Ambrosial odours, such as musk and ambergris.
4. Alliaceous odours, such as chlorine, sulphuretted hydrogen, asafoetida.
5. Goaty odours, such as cheese, cat's urine, rancid oil.
6. Repulsive odours, such as *hyoscyamus* and many of the family of the deadly nightshade.
7. Nauseating odours, such as those of fæces (skatol), putrid flesh, etc.

The sense of smell may be tested by Zwaardemaker's olfactometer. This is a porous tube surrounding a glass tube. The glass tube passes through a screen and is bent upwards to fit the nostril. The porous tube is moistened with a dilute solution of the substance to be tested, and is then moved away from the screen so that it projects beyond the glass tube. The distance that the air

must pass through the porous tube in order to take up enough volatile material to produce a sensation of smell is a measure of the acuity of smell.

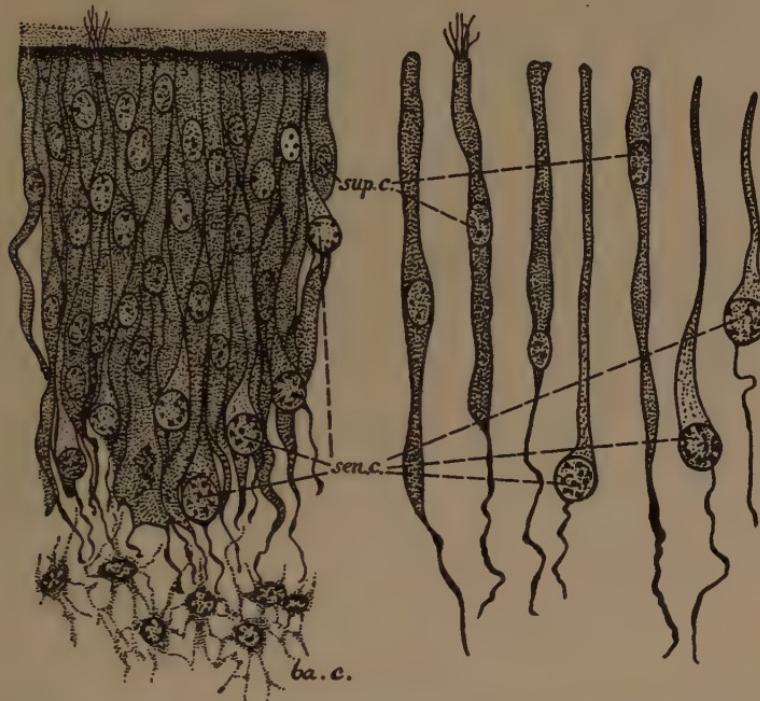


FIG. 189.—Section of Olfactory Epithelium of the Fowl (redrawn from Dahlgren and Kepner).

*sup.c.* = supporting cells, *sen.c.* = sensory cells, and *ba.c.* = basal cells.

Another method that can be used to test the delicacy of the sense of smell is to take a known quantity of a substance, evaporate

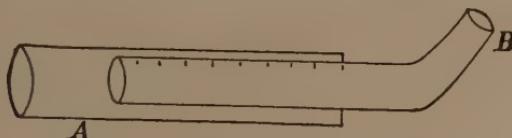


FIG. 190.—Zwaardemaker's Olfactometer.

A porous tube *A* surrounds an impervious tube *B*. According to the distance that *A* projects beyond *B*, more or less of the odorous substance will evaporate into the air passing through the tubes.

it into a known volume of air and breathe a definite quantity of the mixture. The following table shows the minute quantities which can give rise to a sense of smell :—

TABLE L

## DILUTIONS AT WHICH SOME SUBSTANCES CAN BE SMELT (PASSY)

| <i>Substance.</i>         | <i>Dilutions in mgms. per litre.</i> |                     |  |  |  |  |
|---------------------------|--------------------------------------|---------------------|--|--|--|--|
| Orange essence . . . . .  | .                                    | 0·0005 to 0·001     |  |  |  |  |
| Ether . . . . .           | .                                    | 0·0005 to 0·005     |  |  |  |  |
| Camphor . . . . .         | .                                    | 5                   |  |  |  |  |
| Vanillin . . . . .        | .                                    | 0·05 to 0·0005      |  |  |  |  |
| Artificial musk . . . . . | .                                    | 0·00001 to 0·000005 |  |  |  |  |

There is no mechanism in the nose for finding the direction from which a smell comes, but the source of smell can only be detected by finding where it seems strongest.

As one nerve ending might suffice for each separate kind of smell we can understand that there has not been the same classification into a few simple forms as in other sensory end organs. The central connections are through the olfactory tract. Many animals, e.g. dogs and sheep, have a much greater sensitivity to smell than man. Such animals have a greatly developed area (pyriform lobe) at the inferior temporal area which is that part of the cortex to which the olfactory tract can be traced. It is therefore not unreasonable to ascribe the interpretation of smell to this area.

## CHAPTER XXX

### THE EYE AND VISION

The sensation of vision is associated with a receiving organ, the eye, which is an optical instrument ; we must therefore study the formation of images by lenses.

The most important fact in connection with the formation of images is that a ray of light in a medium of greater refractive index travels more slowly than when in a medium of less refractive index. If a ray passes obliquely into a medium of greater refractive index the first portion to enter is retarded, with the result that the ray is bent (refracted) towards the normal to the surface. The refractive index is the ratio of the sine of the angle that the entering ray makes with the normal to the sine of the angle that the ray makes to the normal whilst in the medium or  $\mu = \frac{\sin a}{\sin b}$  where  $\mu$  = the refractive index and  $a$  and  $b$  are the angles of incidence and refraction respectively.

On leaving the medium of greater refractive index the ratio between the sines of the angles is the reciprocal of the ratio when entering ; the emergent ray is therefore bent away from the normal to the surface. If the material has parallel surfaces the emergent ray is parallel to the entrant ray, but if the surfaces are not parallel the emergent ray passes out at some angle to the entrant ray. By preparing curved surfaces so that axial parallel rays falling on them all pass through or diverge from a common point lenses are formed and the common point is called the focus. Non-axial rays do not focus on the optical axis, i.e. the line through the centre of the optical system, but they focus at the same distance from the lens ; the series of foci thus formed fall on what is called the focal plane.

In making diagrams to show how images are formed by lenses we can use the following conventions (Gauss and Listing) :—

1. There are two Principal Planes, anterior and posterior, such that a ray reaching one of them may be drawn from the other at the same distance from the optical axis and on the same side of that axis (unit magnification).

2. There are two Focal Planes, anterior and posterior. A pencil of rays diverging from a point on the anterior focal plane will pass out from the posterior principal plane as parallel rays and

a pencil of parallel rays incident on the anterior principal plane will converge from the posterior principal plane to a point on the posterior focal plane and vice versa.

3. There are two Nodal Points such that a ray reaching one may be drawn from the other parallel to its original direction.

For thin lenses the two Principal Planes and the two Nodal Points may be combined to form one of each.

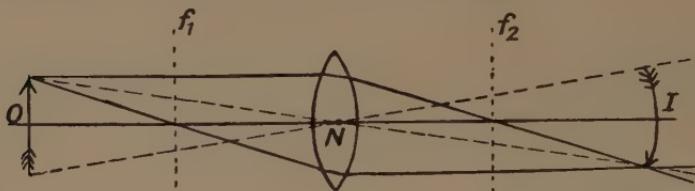


FIG. 191.—Formation of Images by Convex Lens.

$O$  = object,  $I$  = image,  $f_1$  and  $f_2$  = focal planes,  $N$  = nodal point.

It is easier to draw images on the optical axis, but a similar construction can be used for non-axial rays. Thus in Fig. 191 to find the image of an object with a convex lens draw straight lines from each end of the object through the nodal point. Next draw a line from one end of the object parallel to the optical axis. This ray will bend inwards to pass through the posterior focal plane at the optical axis. Finally draw a third line from the same point through

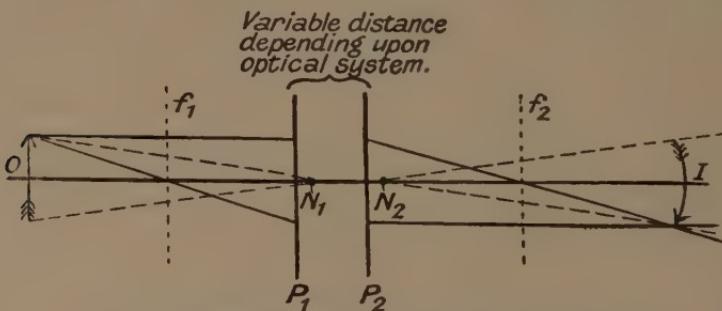


FIG. 192.—Formation of Image by Thick Lens.

$O$  = object,  $I$  = image,  $f_1$  and  $f_2$  = focal planes,  $P_1$  and  $P_2$  = principal planes,  $N_1$  and  $N_2$  = nodal points.

the anterior focal plane where it meets the optical axis ; from the point where the line meets the lens draw the emergent ray parallel to the optic axis. With a good lens these three emergent rays should pass through a common point which gives the image of the point from which the rays originate. Other parts of the object can be drawn in the same way to give the complete image, but any two of the above three lines are sufficient to indicate the position of a point of the image.

With a complicated series of refractive surfaces it is possible to simplify the treatment by the conventions mentioned on page 389. Fig. 192 illustrates the method of construction when the principal planes and nodal points are separated as in thick lenses.

With simple lenses the image is usually curved; with thick lenses a correction may be applied to produce a flat field. Figs. 191 and 192 show uncorrected systems with curved images because that form corresponds to the optical system of the eye.

Applying these considerations to the eye enables us to use Listing's schematic eye (Fig. 193). By the further assumption that the two nodal points can be combined in one and the two principal planes treated as one intermediate plane, the construction is simplified to Listing's reduced schematic eye.

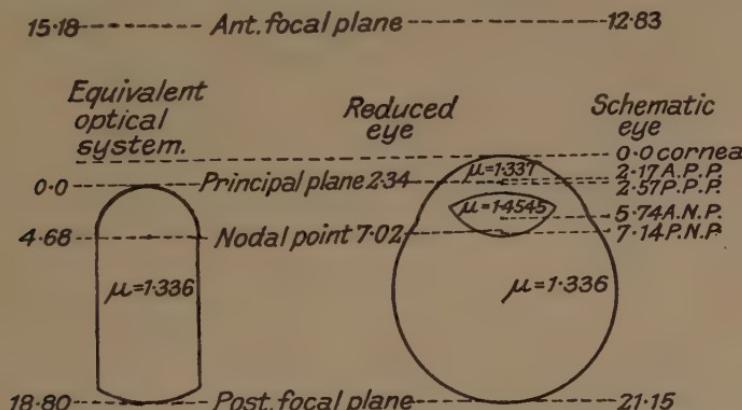


FIG. 193.—Diagram to show the Relations of the Schematic and Reduced Eyes to the Structures of the Eye and a Simple Optical System.

For many purposes the equivalent optical system may be given in round numbers, as Ant.-focal plane 15 mm., nodal point 5 mm., and Post. focal plane 20 mm. from the principal plane. A.P.P. = anterior principal plane, P.P.P. = posterior principal plane, A.N.P. = anterior nodal point, P.N.P. = posterior nodal point. Distances on right are measured from the cornea, and those on the left from the principal plane of the reduced eye. (Measurements from Rivers in Schäfer's *Text-Book of Physiology*.)

The reduced schematic eye is equivalent to a block of material (e.g. glass) with a spherical end, so that there is only one refraction, namely when the rays pass from the air into the glass. An image formed by such a spherical surface would be curved as shown in Fig. 193. This curvature would cause the image to fit the curved retina better than a plane image.

The focal length of a lens is the distance from the posterior principal plane at which all parallel rays meet. If an object is at such a distance that the rays which reach the lens from it are practically parallel the image is formed near the posterior focal plane. If the object is closer so that the rays from it are noticeably divergent the image is formed further from the lens and the image and object are interchangeable, hence these positions are called "conjugate planes."

The strength of a lens is expressed in dioptres, which is the reciprocal of the focal length in metres.

TABLE LI  
STRENGTH OF LENSES

|   |                                     |
|---|-------------------------------------|
| Distance of Focal Plane in Metres . . . . . | 4, 2, 1, 0.5, 0.25                  |
| Strength of the Lens in Dioptres . . . . .  | $\frac{1}{4}, \frac{1}{2}, 1, 2, 4$ |

The relation between the focal length of a lens and the position of conjugate planes is expressed by the formula :—

$$\frac{1}{v} = \frac{1}{f} \pm \frac{1}{u}$$

Where  $f$  = the focal length,  $v$  = the distance of the posterior and  $u$  = that of the anterior conjugate planes. When  $u$  is infinity  $\frac{1}{u}$  becomes zero, therefore the image of a distant object is practically at the focal plane of the lens. For objects where  $\frac{1}{n}$  has a measurable value the image must be behind the focal plane. We shall see later that in the eye the focal length decreases when one looks at a near object, with the result that such images may still be focussed on the retina.

That the anterior surface of the cornea is the main refractive surface in the eye can be shown by the following experiment. Look downwards through a flat-bottomed glass vessel containing water. Focus on some object below the vessel. Then immerse the face in the water, when the object will appear blurred. The refractive index of water is so near that of the cornea that the refraction of the rays is much less than when the light has to pass from air to the cornea.

The eye behaves as a block of material such as is illustrated in Fig. 193, but it has included in it a convex lens. For some purposes one speaks of a reduced schematic eye, but the actual structure of the eye should not be forgotten.

### Structure of the Eye

The eye consists of portions of two co-axial spheres, of which the posterior has the larger radius and is opaque : the anterior has a smaller radius and is transparent to allow light to pass in to reach the sensory layer inside.

The outer coat is formed of dense connective tissue which acts as a protection. The posterior outer coat is known as the sclerotic coat and it is formed of white connective tissue. The anterior outer coat, known as the cornea, consists of special transparent connective tissue which does not contain blood-vessels. The connective tissue cells are special branched cells—the corneal cor-

puscles. The anterior surface of the cornea is covered by a stratified epithelium and the posterior surface has a layer of elastic tissue known as Decemet's membrane, behind which is a layer of cubical epithelial cells.

It is partly due to the thick outer wall that the shape of the eye is maintained. The pressure in the eye distends its walls so that a firm body is produced; it is extremely difficult to produce good optical images with an excised flabby eye.

The second coat of the eye is pigmented. At the back it is called the choroid coat, which is a highly vascular layer containing a black

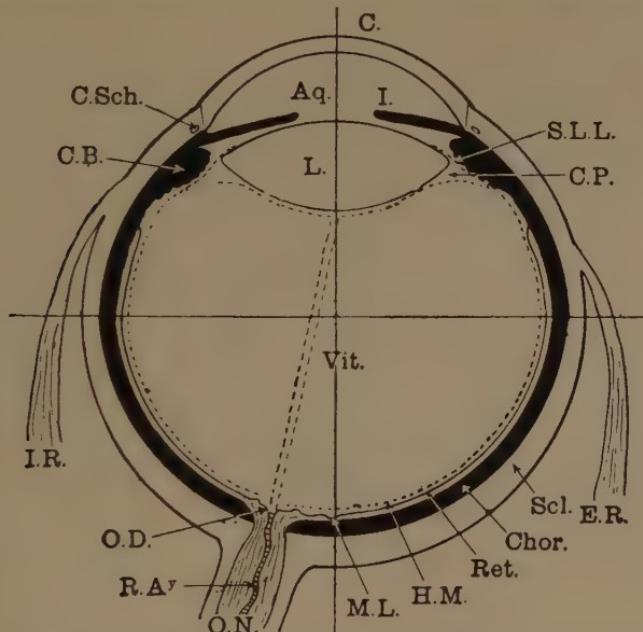


FIG. 194.—Horizontal Section of Eyeball (Parsons and Wright).

C., cornea; Aq., aqueous humour; I., iris; S.L.L., suspensory ligament of lens; C.P., canal of Petit; E.R., external rectus; Scl., sclerotic; Chor., choroid; Ret., retina; H.M., hyaloid membrane; M.L., macula lutea; O.N., optic nerve; R.Ay., retinal artery; O.D., optic disc; I.R., internal rectus; Vit., vitreous humour; C.B., ciliary body; C.Sch., canal of Schlemm; L., lens.

pigment. The optical importance of this pigment is that it stops light from passing through the exposed parts of the sclerotic into the eye, and it limits internal reflection on the inner surface of the eye. The anterior part of the choroid layer is separated from the cornea and forms a diaphragm, the iris, which narrows the aperture of the eye, leaving a central opening, the pupil. The pupil appears black owing to the absence of reflected light from the inner surfaces of the eye. The iris contains radial and circular muscle fibres.

The third layer of the eye is the nervous portion or retina. It

lines the posterior portion of the eye and its continuation forwards is devoid of all the nerve elements and forms thin membranes.

Where the cornea, sclerotic and iris all meet is a special region called the ciliary region, where there is a muscle known as the ciliary muscle. In front of the lens the eye contains a fluid known as the aqueous humour, which fills the anterior chamber of the eye. Behind the lens the eye is filled by a jelly known as the vitreous humour.

The hyaloid membrane surrounding the vitreous humour is continued forward as two layers, the suspensory ligaments—between which is contained the lens.

**The Retina.** The retina is the nervous part of the eye and it is

responsible for the conversion of light stimuli into nerve impulses. It contains ten layers, as follows :—

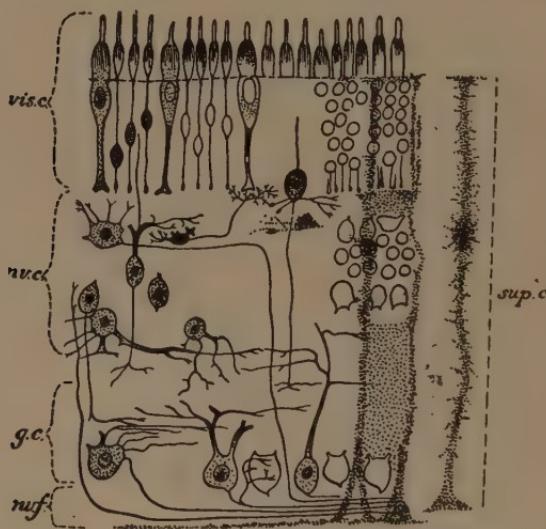


FIG. 195.—Diagram of the Retina in Man (Dahlgren and Kepner).

vis.c., layer of visual cells (rods and cones), the nuclei and processes forming the outer nuclear layer; nuc., layer of bipolar cells, the inner of which form the inner nuclear layer; g.c., ganglion cells, forming the ganglion cell layer; nuf., nerve-fibre layer; sup.c., supporting or neuroglia cells.

must pass through all the layers of the eye, namely the sclerotic choroid and the remaining layers of the retina. It enters on the inner side of the optical axis and below the horizontal plane through that axis (*the blind spot*).

3. A layer of ganglion cells, from which the optic nerve fibres arise and pass towards the brain. In this layer are contained the retinal blood-vessels. The blood supply of the retina comes in by the arteria centralis retinæ. This sends off radiating branches which ramify over the whole of the anterior surface of the retina.

4. A layer of synapse connections (dendrons)—the inner molecular layer—linking the ganglion cells with the succeeding layer.

1. An internal limiting membrane which lines the retina and separates it from the vitreous humour.

2. A layer of optic nerve fibres which spread over the whole of the retina except a small area known as the *forea centralis*. To enable the optic nerve fibres to reach this position the optic nerve

5. A layer of nerve cells, the inner nuclear layer.
6. A second synapse layer, the outer molecular layer.
7. A layer of nerve cells, the outer nuclear layer.
8. An external limiting layer.
9. A layer of specialized structures known from their shapes as rods and cones. The cell bodies to which these structures belong are situated in the outer nuclear layer. The rods are thinner and longer than the cones and they contain a pigment known as rhod-

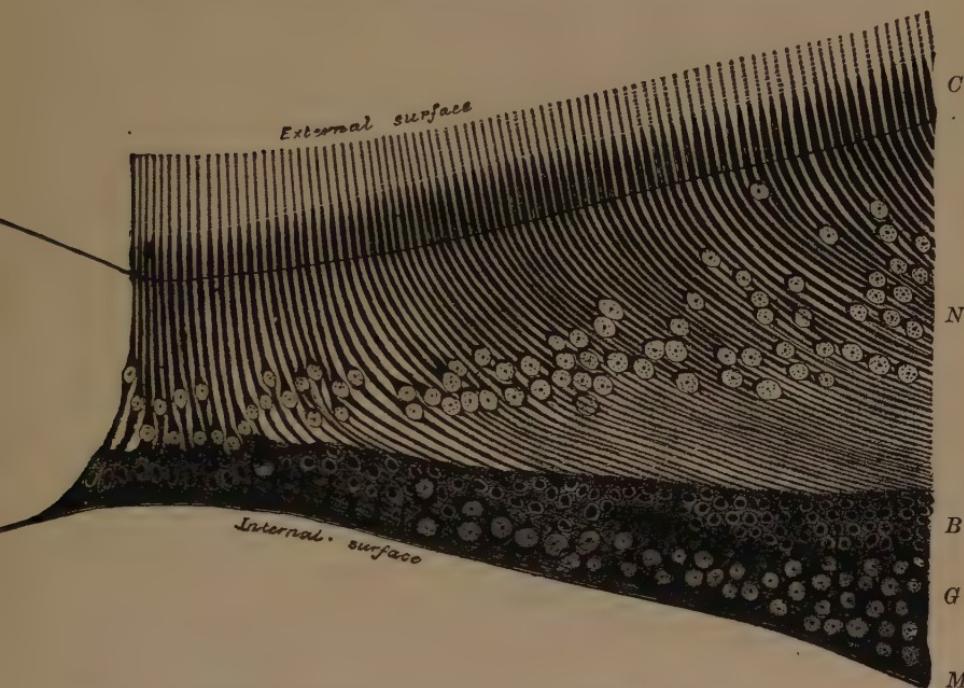


FIG. 196.—Diagram of the Arrangement of the Retinal Elements at the Fovea Centralis.

*M* = bases of Müllerian fibres, *G* = ganglion cells, *B* = nuclei of inner granules (bipolars)  
*N* = cone-fibre nuclei (outer granules), *C* = cones. (From Quain's *Anatomy*, Longmans, Green & Co.)

opsin. Both rods and cones have been described as being built up of a series of discs but the laminated appearance may be the result of the method of preparation.

10. A layer of cells containing pigment. These cells are mobile so that the pigment may be either spread out to lie between the rods and cones or retracted to lie against the choroid coat, leaving the rods and cones exposed.

There are certain special supporting cells, cells of Müller, the expanded ends of which form the inner and outer limiting membranes. In the inner nuclear layer are cells known as Amacrine cells, as they have no recognizable axon or dendrons.

Each cone links up ultimately with a separate ganglion cell, whilst several rods connect with a single ganglion cell. The axis of symmetry of the eye (optical axis) does not correspond with the visual axis of the eye.

If the retina be examined where the visual axis of the eye passes through it there will be noticed a special feature, namely a depression, the fovea centralis, surrounded by a yellow ring, known as the macula lutea, the yellow pigment of which is generally described

as being diffused through the layers of the retina, but not in the layer of rods and cones. This depression is characterized by an absence of nerve fibres and an oblique arrangement of the other layers, so that at the central part most of the layers have disappeared and practically only the layer of rods and cones is left.

*The Ophthalmoscope.* If one wishes to examine the condition of a living eye one must arrange some means of illuminating its interior. In order to do this and at the same time see into the illuminated eye one uses the ophthalmoscope, the essential feature of which is an obliquely placed mirror with a central hole for the observer to see through. In this way light is reflected into the observed eye and yet the observer's eye is opposite the pupil of the observed eye, and is thus able to see the illuminated interior. There are



FIG. 197.—Various Forms of Ophthalmoscope.

In I a small figure indicates the focal power in dioptres of the lens which is in front of the opening. II and III are the front and back views respectively of the same instrument. By turning the lower disc in III a series of lenses are rotated to lie behind the opening in the ophthalmoscope mirror. The focal length of the lens so placed is shown by a figure in the central square aperture, + indicating a convex lens and — a concave.

two ways of employing the ophthalmoscope, namely the direct and indirect methods.

The Direct Method is illustrated in Fig. 198. The rays from a source of light are reflected by the concave mirror and illuminate the retina of the observed eye. If the observed eye is normal (emmetropic) and the accommodation is relaxed, rays from any illuminated part will pass out as parallel rays through the opening in the concave mirror. If the observer's eye is normal or properly

corrected by lenses and his accommodation is relaxed, the parallel rays will be focussed on his retina and he will see the retina of the observed eye. If the observed eye is not emmetropic lenses can be introduced behind the mirror until a clear image of the retina

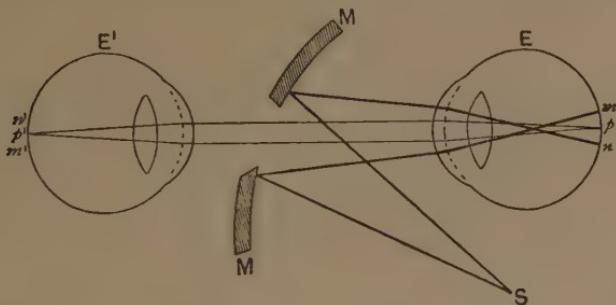


FIG. 198.—Ophthalmoscope—to show the Formation of the Image in the Direct Method (Noël Paton).

The rays from light S are reflected by the mirror MM into the eye E illuminating the area  $m_1$ . A point  $p$  will project rays which pass out parallel through the opening in the mirror and are focussed by the eye  $E'$  at  $p'$ .

is obtained. In this way the lens necessary to correct any defect in the observed eye can be determined.

The Indirect Method is shown in Fig. 199. The light is reflected by a concave mirror as in the direct method, but a convex lens is

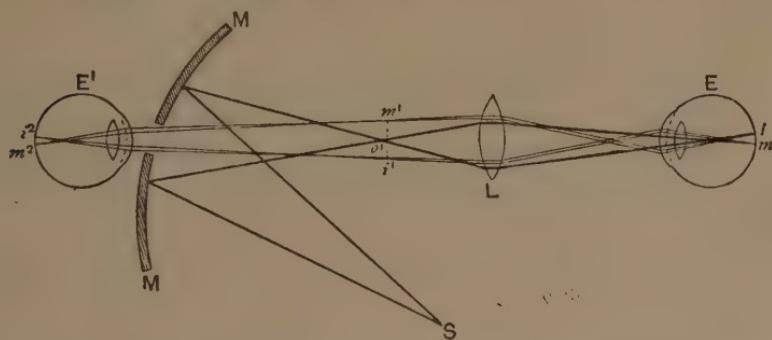


FIG. 199.—Ophthalmoscope—to show the Formation of the Image in the Indirect Method (Noël Paton).

The rays from the light S are reflected by the mirror MM through lens L into eye E. Rays from the retina of E pass out and are focussed by the lens to form an image of  $l^1m^1$  at  $l^2m^1$ : this image is focussed by eye  $E'$  at  $l^2m^2$ .

interposed in the path of the rays. Rays from the illuminated area of the retina are focussed to form an inverted image between the lens and the observer's eye. This inverted image is focussed by the observer. The image seen is inverted and a larger area of the retina is visible than can be seen at one view by the direct method.

When the interior of the eye is examined one sees an orange-coloured field on which may be observed the radiating retinal blood-vessels, the pale area where the optic nerve pierces the retina and the fovea centralis. The macula lutea may also be recognized in some cases as a darker area surrounding the fovea centralis.

**Sensitive Layer of the Retina.** The optic nerve fibres are not directly sensitive to light, so that where the optic nerve pierces the retina there is a *blind spot*. This blind spot can be demonstrated by Mariotte's experiment, which is illustrated in Fig. 200. The left eye is closed and one looks at the ●, the figure is moved towards and away from the eye, and at about the distance of six inches the gap in the line disappears. As the figure is moved nearer, the gap in the line moves peripherally on the retina and will lie to the nasal side of the blind spot. The reverse movement causes the image to move inwards so that the gap will lie to the temporal side of the blind spot. In carrying out this experiment it is essential that the ● be kept focussed on the fovea, as the least movement of the eye will cause the image of the gap to move off the blind spot. By

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FIG. 200.—Mariotte's Experiment to demonstrate the Blind Spot  
(Flack and Hill).

When held about 6 in. away with left eye closed, and on looking at the ●, the line on the right appears continuous. As it is difficult to focus the image at this distance, it is better to do the experiment with a larger figure at a greater distance from the eye.

measuring the distance of the object from the eye and the area of the object which disappears, as the distance of the retina from the nodal point is known, it is possible, by the principle of similar triangles, to calculate the position and area of the blind spot. It will be found that the blind spot corresponds to the entrance of the optic nerve.

The sensitive layer lies behind the retinal blood-vessels. Thus, on looking at a brightly illuminated surface, e.g. a white cloud, through a small pin-hole, it is found that by giving a rotary motion to the pin-hole the branching blood-vessels can be seen as shadows. These shadows can be used to prove that the sensitive layer of the retina is that of the rods and cones, and a diagram illustrating the experiment is given in Fig. 201. If a strong light is projected through the margin of the sclerotic and the eye be directed at a plain surface, the retinal blood-vessels will be seen like a vine on that surface. If the light be moved a known distance and the distance which the image of a definite blood-vessel appears to move is measured, the distance of the sensory layer behind the blood-vessels can be calculated.

The method of calculation is based on the ratios between the sides of similar triangles. The distance  $A'-B'$  is to  $a-b$  as the distance of the screen from the nodal point is to that of the retina from the nodal point: the latter distances can be measured from the distance of the screen from the eye and the known constants of the eye. Having determined the distance  $a-b$  the distance of the vessel from the retina, which can be represented by  $x$ , can be calculated. The total diameter of the eye is known and can be represented as  $y$ . The distance that the light traverses on the sclerotic, i.e. the intersection of the lines to A and B, with the sclerotic, can be measured, and for brevity we shall write it  $A-B$ . Therefore  $a-b : A-B :: x : y-x$ . By combining this with the ratio for the determination of  $a-b$  we can calculate  $x$  from the experimental data, namely, extent of apparent movement on screen, distance of screen from the eye, extent of movement of illuminated area on sclerotic and the known constants of the eye.

By such measurements it has been calculated that the sensitive layer is 0.19 to 0.33 mm. behind the blood-vessels, and by histological measurements the layer of rods and cones is found to be 0.2 to 0.3 mm. behind the vessels; therefore we believe that the rods and cones are the percipient elements of the retina.

The above proof that the rods and cones are the elements of the retina sensitive to light is in agreement with the fact that they are specialized structures found only in the retina, whilst the other retinal elements are not peculiar to the eye. Also at the part of the eye where definition is most acute (*fovea centralis*) the layers of the retina are thinned out so that only a few cells are present in addition to the rods and cones (see Fig. 196). As will be described later a special light-absorbing material is present in the layer of rods and cones. This is further evidence that the rods and cones are the sensitive elements of the retina.

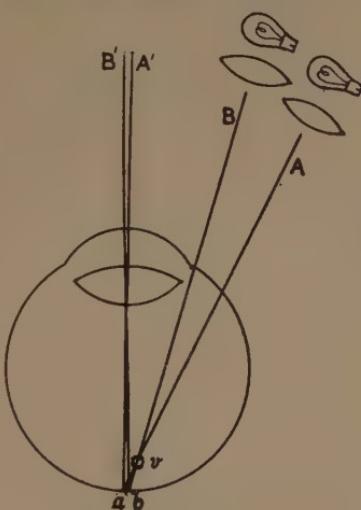


FIG. 201.—Purkinje's Shadows  
(Alex. Hill).

A beam of light traversing the eyeball in the direction A throws a shadow of the vessel  $v$ , lying on the front of the retina, upon the sensitive layer at its back. When the light is moved from A to B the shadow moves from  $u$  to  $v$ . The mind, supposing the shadow to be a dark mark on the nearest wall or screen, infers that this mark moves from  $A'$  to  $B'$ .

### SUPERICAL AND CHROMATIC ABERRATIONS

These two faults are present in all optical systems but they may be reduced to negligible proportions in various ways.

Spherical aberration is due to the fact that the rays falling on the peripheral portion of a lens are always focussed in front of those coming through the central region. This spherical aberration tends to produce blurred images and the blurring becomes more marked the greater the curvature of the lens. This defect can be reduced by limiting the rays to the central part of the lens.

It is one of the functions of the iris to restrict the rays to the more central part of the optical system. In the eye the central part of the lens has a greater refractive index than the peripheral portion: this difference diminishes the spherical aberration of the system.

It is true that a lens can be ground so that spherical aberration is unimportant provided the rays of light always reach the lens at the same angle either divergent or convergent, but if the rays came at a different angle the spherical aberration would be either over or under corrected.

*Chromatic aberration* is due to the different refractive indices for lights of different wave lengths. In general the shorter wave lengths are deflected more than the longer ones, thus violet and blue rays are focussed in front of red rays. This tendency for images to be surrounded by coloured fringes can be shown in the eye. If one looks through a pin-hole covered by several thicknesses of cobalt glass at the incandescent filament of a metallic-filament electric lamp, two filaments will be seen, one red and the other blue. The cobalt glass cuts out the intermediate rays so that one does not see a blurred image with coloured fringes. Further, if the red image is in focus the blue one is blurred and vice versa.

Chromatic aberration is decreased by using compound lenses so that the dispersion by one lens is corrected by dispersion in the opposite direction by a second lens, and yet the deviation of rays is not corrected, so that an object can be focussed by the compound lens. This correction is possible because the deviation and dispersion by different materials are not always proportional to each other. A lens so corrected is an achromatic lens.

Another way of eliminating chromatic aberration is by using monochromatic light. It is possible that the pigment of the macula lutea may decrease the effect of chromatic aberration by absorbing the blue rays before they reach the rods and cones. The influence of the yellow spot in absorbing blue rays is shown by looking at a

bright sky through some coloured object which absorbs the middle of the spectrum (e.g. a solution of chrome alum or methyl violet). The red and blue rays are transmitted, giving a purple colour, but where the macula lutea absorbs some of the blue rays a rosy area will be seen.

*Scheiner's Experiment.* In order to show that the focus of the eye alters the following experiment should be carried out (see Fig. 202). Arrange two pins so that one is about a foot from the eye and the other about three feet away. Look at these through a diaphragm held close to the eye with two pin-holes close together in it, i.e. less than the diameter of the pupil apart. If one looks at the near pin the far one appears double, and if one of the holes in the diaphragm is closed the image which appears to be on the same side as the hole which is occluded disappears. If now one looks at the far pin the near one appears double and closing one hole causes the image which appears to be on the opposite side to disappear.

This experiment shows that on looking at a near object distant objects are focussed in front of the retina, and if sharp images are obtained by using two pin-holes the rays cross and form double images. On looking at a more distant object the focal adjustment of the eye alters so that a near object would be focussed behind the retina ; by producing sharp images as before by pin-holes the double images are seen. This experiment also helps to show that images on the retina are inverted, but that we see them right way up by a process of association with other sensations. Thus on looking at the near object the image of the distant object disappears on the same side as the occluded hole. The image is actually formed on the opposite side of the retina as the rays have crossed. On the contrary when looking at a far object the rays from a near object have not crossed, hence, as we refer images to the opposite side, on occluding one hole the image which disappears is believed to be on the opposite side.

Other proofs that images are inverted on the retina are firstly those due to our knowledge of the formation of images by lenses. Scheiner's experiment is one of those which depends on a knowledge of optics. Another proof depending on a knowledge of optical

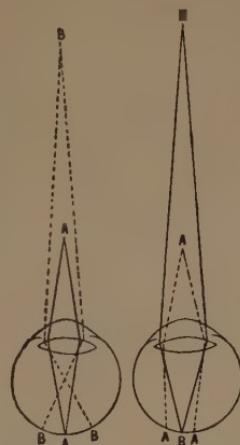


FIG. 202.—Diagram of Scheiner's Experiment (Flack and Hill).

A = when looking at the near pin, the rays from the far pin cross and form two images on the retina, one from each hole in the card.  
B = when looking at the far pin, the rays from the near pin do not focus on the retina but form two images, one from each hole in the card.

laws is to look through a pin-hole held close to the eye and push the head of a pin upwards across the hole. As the object is within the anterior focus of the eye its image would be formed behind the retina, hence its shadow is upright on the retina. The pin appears to come down from above owing to our habitual inversion of retinal images.

Further evidence is obtained by using the eye of an animal. An ox eye is obtained from the slaughter house and a window cut in the sclerotic. The images of external objects focussed on the retina of this eye can be seen where the sclerotic is removed, and they are found to be inverted.

### Focal Adjustments of the Eye

In order to produce sharp images the objects must be focussed. In a camera this is accomplished by changing the distance between the lens and the screen. For near objects the screen must be farther from the lens than for far objects (cf. conjugate planes, p. 391). Another method is to use a lens of greater curvature for near objects, and some "fixed focus" cameras are furnished with an extra lens

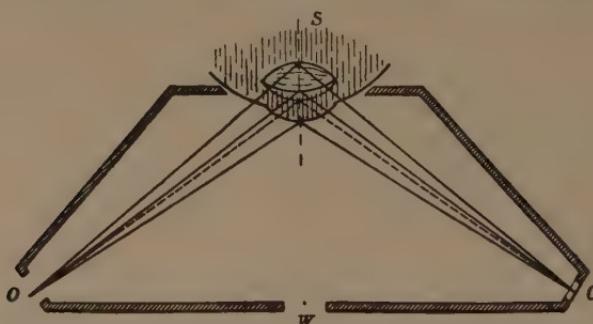


FIG. 203.—Diagram of the Course of the Rays of Light in the Phakoscope.  
O = opening for observer's eye, S = eye of subject, C = source of light, and W = window through which subject may look at a distant or near object.

for near objects ("portrait attachment"). The latter is the main principle used for changing the focus of the human eye.

*Sanson's Images and the Phakoscope.* The proof that the lens changes its curvature when looking at objects at different distances is by means of Sanson's images. These are the reflections from the anterior surface of the cornea, the anterior surface of the lens and the posterior surface of the lens. These images are rendered visible by a dark box called the phakoscope, which cuts off extraneous light.

In Fig. 203 the observed eye is at the aperture S, looking through the opposite aperture W at a distant object. A source of light

at one side C is reflected from the observed eye to the observer's eye at aperture O. The source of light is frequently duplicated by prisms so that the observer sees double images. Three pairs of images are seen: the first small, erect, and bright from the anterior surface of the cornea; the second large, dim, and erect from the anterior surface of the lens; and the third, small, inverted and intermediate in distinctness, is from the posterior surface of the lens.

When the observed eye is focussed on a new object held close to aperture W the first image remains unchanged, the third image is very slightly changed, but the second image becomes smaller and approaches the first, thus showing that the anterior surface of the lens becomes more curved and that it approaches the cornea.

TABLE LII

CHANGES IN CURVATURE OF LENS AND FOCAL LENGTH OF EYE  
(HELMHOLTZ)

|                                  | <i>Curvature of Surface of Lens.</i><br>Anterior. | <i>Posterior.</i> | <i>Focal Length</i><br>(approximately). |
|----------------------------------|---|-------------------|---|
| Resting eye . . . . .            | 10 cm.  | 6 cm.             | 19 mm.                                  |
| Eye accommodated for near vision | 6 cm.   | 5 cm.             | 17 mm.                                  |

Thus we see that *accommodation*, which is the adjustment of the eyes to focus near objects, is accompanied by an increase in curvature of the lens and a slight movement of the lens forward away from the retina.

The increased curvature of the lens will produce greater spherical aberration, but this is compensated by narrowing of the pupil by the iris, which limits the path of the rays to the central part of the lens. A third factor in accommodation is that if two eyes are to focus the same object on the foveæ centrales the eyes must become convergent during near vision.

As mentioned on p. 392 the main factor in focussing images is the anterior surface of the cornea, but for the finer adjustments concerned with near and distant vision the lens is the active agent.

**Mechanism of Movements of Lens.** When the lens is re-

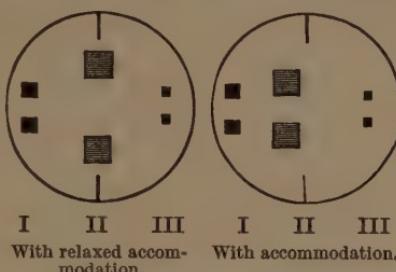


FIG. 204.—Sanson's Images. I, From Anterior Surface of Cornea. II, From Anterior Surface of Lens. III, From Posterior Surface of Lens.

During accommodation II becomes smaller and approaches I, showing increased curvature of anterior surface of lens, and that this surface approaches the cornea, i.e. moves forward (from Waller's *Human Physiology*, Longmans, Green & Co.).

moved from the eye it takes the shape that it possesses during near vision. In the resting eye the lens is flatter and it is held flatter by some process which does not involve muscular activity. This is brought about by the suspensory ligament which is attached to the anterior and posterior surfaces of the lens. By a pull on the two ends the lens is squeezed flat between the two layers of the suspensory ligament. The pull on the suspensory ligament is due to the fact that it is continuous with the retina and the pressure of the vitreous keeps it on the stretch. During accommodation the pull is relaxed and the lens becomes more convex by its own elasticity. The relaxation of the suspensory ligament is produced by the ciliary muscle.

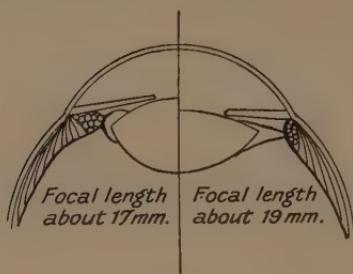


FIG. 205.—Diagram to show the Changes that take place in the Eye during Accommodation.

The right half represents the eye relaxed for distant vision, and the image is formed on the retina, which practically coincides with the focal plane about 19 mm. behind the principal plane of the reduced eye. The left half shows the condition during accommodation. The radial fibres of the ciliary muscle pull the suspensory ligament forwards and the circular fibres pull the ligament inwards so that the suspensory ligament is relaxed. The lens becomes more curved and bulges forward by its own elasticity. At the same time the iris extends inwards to narrow the pupil. The focal plane is in front of the retina so that the image of near objects is formed on the retina. The circular fibres of the ciliary muscle are markedly hypertrophied in hypermetropic eyes.

two reciprocal innervations, i.e. contraction of one group is accompanied by relaxation of the opposing fibres. Stimulation of the cervical sympathetic causes dilation of the pupil by contraction of the radial fibres, while stimulation of the third nerve causes constriction of the pupil by contraction of the circular fibres. Cutting of these nerves causes the reverse changes.

The movements of the eyes themselves depend on the extrinsic muscles and they are mainly supplied by the third nerve.

### Common Defects in the Eye

If the images of external objects are not sharply focussed on the layer of rods and cones defective vision results. The normal range

*The Ciliary Muscle* consists of two portions: radial fibres arising at the sclero-corneal junction and running towards the retina, to be inserted into the suspensory ligament, and circular fibres forming a ring round the eye. The radial fibres pull the suspensory ligament forwards. The circular fibres by forming a narrower ring pull the suspensory ligament inwards. Thus the increased curvature of the lens is the result of relaxation of the suspensory ligament due to the contraction of the ciliary muscle which is innervated from the third cranial nerve.

*The Iris* is composed of circular and radial muscle fibres with

of vision is from 15 cm. to infinite distance and this range is brought about by the process of accommodation described above. If, however, objects closer than 15 cm. can be sharply focussed and distant objects are indistinct, then the eye is *myopic* or short-sighted. This defect is due to a tendency for objects at normal distances to be focussed in front of the retina so that even with relaxed

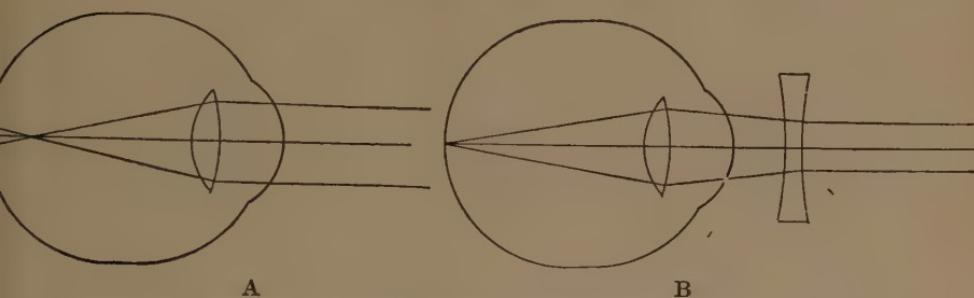


FIG. 206.—Diagram showing Course of Rays in Myopic Eye (Rowlands' *Hygiene for Schools*).

A = parallel rays, B = rays rendered divergent by concave lens.

accommodation distant objects are focussed before the rays reach the retina. Near objects, owing to the divergent rays from them, are focussed further back. Of the two possible causes of this defect, namely, too great a focussing power of the cornea and lens, and too great a distance between the lens and retina, it is the latter which is usually found. The length of the normal eye is about 2·5 cm.

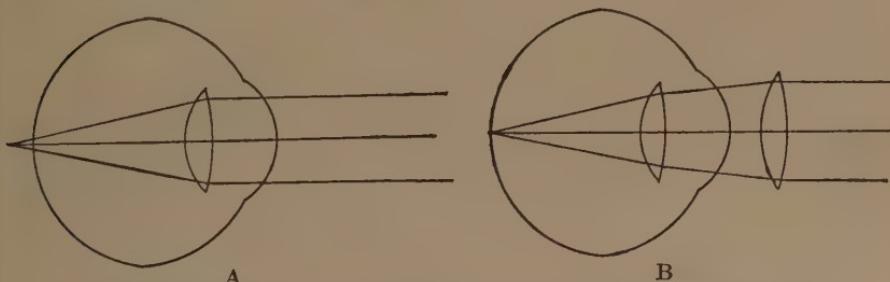


FIG. 207.—Diagram showing Course of Rays in Hypermyopic Eye (Rowlands' *Hygiene for Schools*).

A = parallel rays, B = rays rendered convergent by convex lens.

and the greatest length of a myopic eye may be as much as 3·4 cm. To enable these individuals to see objects at a reasonable distance the rays coming from them must be made more divergent and this is accomplished by the use of a concave lens in front of the eye.

The opposite condition where the eye is too short is known as *hypermetropia*. The shortest hypermetropic eye on record is about 1·6 cm. from front to back. In this condition distant objects

can be focussed on the rods and cones by means of accommodation, but near objects cannot be so focussed even with the greatest effort of accommodation, and therefore a convex lens must be used to shorten the focal length of the eye plus the lens.

In older people, even those who originally had good vision, the

near point recedes. This is due to a loss in the power of accommodation and the main defect is loss of elasticity of the lens, so that it does not become sufficiently convex. An individual suffering from a mild degree of hypermetropia will notice the effect of the sclerosis of the lens sooner than one with some myopia. This defect is called *presbyopia* and it is remedied by the use of convex lenses for near vision.

Another defect is *astigmatism*, which is due to unequal curvature of the cornea. Thus the focus for rays in the plane of greater curvature lies in front of that for rays passing through the plane of lesser curvature, with the result that distortion of objects occurs. A

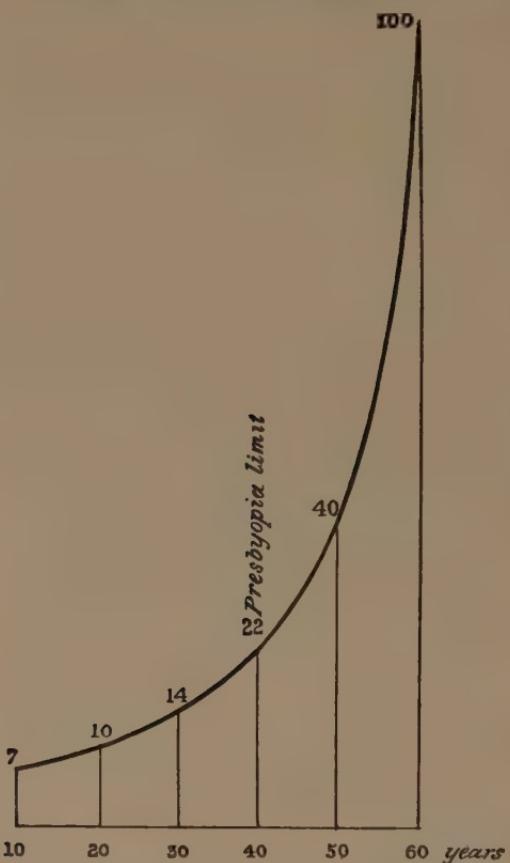


FIG. 208.—Recession of Punctum Proximum (Near Point) with Increasing Age.

Ordinates in mm. represent the distance of the near point in cm. When the "near point" is further than 22 cm. presbyopia is said to be present. Usually this occurs about the age of 40 (from Waller's *Human Physiology*, Longmans, Green & Co.).

series of radial lines cannot all be focussed at the same time because if the eye is accommodated so that lines in one plane are in focus the lines at a different angle will be indistinct. The remedy is to use a cylindrical lens to compensate for the unequal curvature of the cornea, and if other defects are also present to combine the two corrections by suitable grinding of a single lens. Irregular astigmatism

also occurs, but it does not interfere with vision in the same way, as it is due to local irregularities in the cornea.

A rough test for the condition of the optical apparatus of the eye is by means of *Snellen's Test Types*. These consist of letters of various sizes which are viewed at a standard distance. The smallest letters which can be distinctly read furnish data from which the condition of the eye may be judged.

### Visual Judgments

The sensations produced by stimulation of the retina must be interpreted and this interpretation is the result of correlation with other sensations. For instance the images on the retina are inverted but this does not cause any difficulty as the interpretation makes the object appear in its proper position. This is comparable to the experience of photographers or microscopists who do not find any difficulty in the inverted images formed by their respective instruments. One does not notice the inversion when focussing a camera, and one automatically moves the microscope

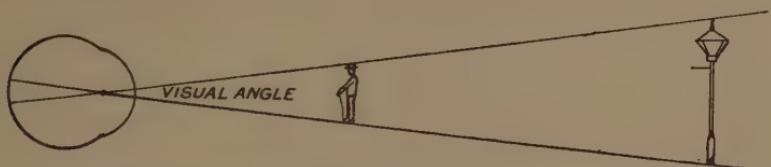


FIG. 209.—Diagram to show how Objects of Different Sizes may Occupy the same Extent of the Retina if they Subtend the same Visual Angle.

slide in the correct direction, although it is apparently the other direction as seen in the microscope.

The shape of an object is judged by the shape of the image on the retina, but the perception of the size and distance of an object is determined as follows :

The area of the retina occupied by an object depends on the size of the object and its distance from the eye. The visual angle is the angle subtended at the nodal point, by an object. Therefore the angle is directly proportional to the size of an object and inversely proportional to its distance from the nodal point. Thus it will be found that if one object is two-and-a-half times as far away as another it will subtend the same angle if it is two-and-a-half times the size of the nearer object. The area of the retina occupied by the image of an object depends upon the visual angle. In Fig. 209 the man and the lamp-post each subtend the same angle, hence they each would extend for the same distance on the retina.

In our visual judgments we find that size and distance are reciprocally related. A good example of this relation will be found in the section dealing with "after-images." In the judgment of distance we are helped by the following factors. There is the effect of atmosphere whereby distant objects are toned down, and it is an extreme case of this which causes objects in a fog to appear large because they are judged to be farther off than they are. If the objects were farther off, the area of the retina stimulated must correspond to a larger object. Objects at different distances may intervene so that the more distant one is partly hidden by the nearer, and this may help in determining their relative distances.

The movement of one object across another when the head is moved is greater for near objects than for more distant ones; this helps in deciding their relative positions. Thus we see that with

a single eye judgments of size and distance depend on several factors. For instance the size of an object may be estimated by its dimensions

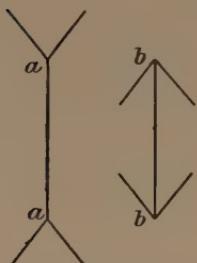


FIG. 210.—The Apparent Lengths of two Equal Lines is altered by the Divergent Lines (Flack and Hill).

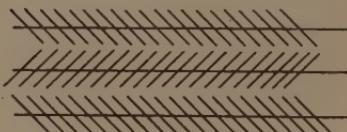


FIG. 211.—Zöllner's Lines. Oblique Lines alter the Apparent Direction of Parallel Lines (Flack and Hill).

Look lengthwise along the lines.

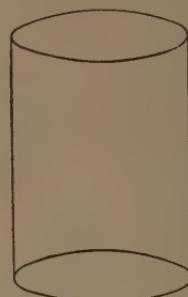


FIG. 212.—This represents a Hollow Cylinder of which the Mouth may be either Upwards or Downwards (Flack and Hill).

relative to those of a known object near it and its distance may be determined by the apparent size of a recognized feature of the landscape.

The effort of accommodation is also a factor in the judgment of distance. The great influence of mental processes in visual perceptions is shown by the large number of optical delusions, of which a few are shown in Figs. 210 to 214.

Fig. 210 illustrates the effect of oblique lines in altering the apparent length of two equal lines. It seems probable that the length is estimated to correspond to a point behind the point of the V instead of at the extreme tip of the same.

Fig. 211 shows the effect of crossing lines in apparently altering the direction of parallel lines.

In Fig. 212 a transparent cylinder is seen with an open end which may be either at the top or at the bottom.

The illustration in Fig. 213 is that of a symmetrical arch which appears asymmetrical when one side is crossed by a pillar in the foreground.

A space divided by a series of objects seems greater than a similar space when empty. This is well shown in Fig. 214.

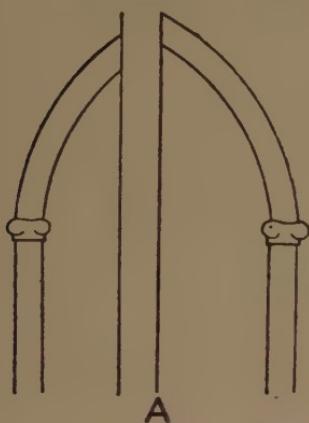


FIG. 213.—A Symmetrical Gothic Arch intersected by the vertical Column A.

It is difficult to believe that the left-hand and right-hand limbs of the arch would meet on the line A (Alex. Hill).

the correspondence is not absolute because the two eyes are separated by approximately six centimetres, therefore the view obtained by each is slightly different from the other. This can be shown in many ways; if one stands, for instance, in front of an upright article, looking down on it so that with the left eye shut it appears upright, then without moving the head close the right and open the left eye, the object will be seen to slant to the right. This difference between the two eyes is a factor in the judgment of solidity and distance in addition to those operating with a single eye. The stereoscope is an instrument for recombining such images with the production of the appearance of solidity.

If two photographs are taken with two lenses which are about six centimetres apart they will be seen to be slightly different in the appearance of their details. The stereoscope is an instrument whereby each of two such photographs are viewed by a separate eye, and the resulting sensation is the appearance of the scene in relief. As shown in Fig. 215 this is

A                      B                      C  
.....

FIG. 214.

The distance from A to B is equal to that from B to C.

**Binocular Vision.** When both eyes are used they are normally so aligned that one central point is focussed on the fovea of each. Objects falling on other parts are said to fall on corresponding points, i.e. those above and to the right of the point of fixation fall below and to the left of the foveæ, but

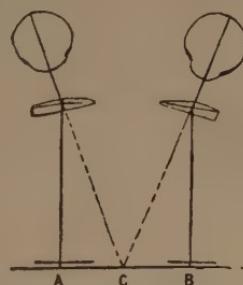


FIG. 215.—Diagram of a Stereoscope (L. Hill).

Two photographs, A and B, are seen at C. The rays of light from A and B are refracted by the prisms into the eyes so that they appear to come from C.

accomplished by two prisms so that the paths of the rays are deviated with the result that the two pictures appear as a single object. Another method of combining separate images is shown in Fig. 216. The figure is viewed with relaxed accommodation so that the eyes are parallel, when the fish will be seen in the tank.

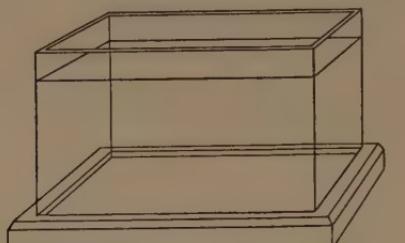


FIG. 216.—To illustrate Haploscopic Vision (Flack and Hill).  
Look at the figure with relaxed accommodation, holding it about 7 in. from the eyes.

This combination of separate images on the two retinae is known as *Haploscopic Vision*, or single vision with two eyes.

*The Horopter* is the line joining all objects which appear as single in binocular vision.

**Visual Persistence.** The effect of stimulation of the retina, like all other physiological processes, shows a latent period, a period during which the sensation develops, and a period during which the sensation disappears. In vision the latent period is very short, but the persistence may be prolonged. The persistence of an image after the stimulation has ceased gives rise to what are called "after-images" which may be either positive or negative. One way of showing visual persistence is to have two objects or alternate letters of a word on opposite sides of a piece of card. A piece of string is tied to the mid-point of each end of the card, and the card is rotated by rolling the pieces of string between the thumb and forefinger of each hand. If a cage is drawn on one side and a bird on the other the bird will be seen in the cage, and in the case of the alternate letters of a word, the word will be seen entire when the card is rotated. It is because of this persistence of vision that a series of pictures can be fused to produce the sensation of movement when presented successively as in the cinematograph. These are positive after-images, i.e. of the same nature as the original object, but if one looks for a long time at an object, and then at a neutral surface, a negative after-image, i.e. one in which light and shade are reversed, is obtained. If the object is a coloured one the colours will be altered in the negative after-image, and to understand this we must now study colour vision.

**Colour Vision.** When daylight is examined by means of a

spectroscope the spectrum is seen to consist of a series of colours shading into each other. These colours correspond physically to a series of wave lengths or frequencies. The wave lengths and frequencies are related through the rate of propagation of light thus :

$$\text{Frequency} = \text{speed}/\text{wave length}.$$

TABLE LIII

## COLOUR, WAVE LENGTHS AND FREQUENCIES OF LIGHT WAVES

| Colour.                            | <i>Red.</i> | <i>Orange.</i> | <i>Yellow.</i> | <i>Green.</i> | <i>Blue.</i> | <i>Violet.</i> |
|------------------------------------|-------------|----------------|----------------|---------------|--------------|----------------|
| Wave lengths (A°.U) about          | 7,000       | 6,300          | 5,900          | 5,600         | 5,000        | 4,250          |
| Frequencies about $10^{14} \times$ | 4.3         | 4.8            | 5.14           | 5.4           | 6.06         | 7.1            |

Now it is not necessary to have different receptors for each wave length as the sensations may be produced by a mixture of a few colours. We must look for the simplest method by which colours can be analysed and the results of the analysis reunited as sensations. It is necessary when dealing with mixtures of colours to distinguish between the results of adding and subtracting colours. Unless one uses a source of pure coloured light such as a narrow region of the spectrum one is really dealing with a mixture of colours.

Coloured objects reflect from white light certain rays. If these rays are absent from the incident rays the colour is absent and the object appears black. A yellow pigment reflects red, yellow and green rays, a blue pigment reflects green and blue rays. Thus in a mixture of the two the red and yellow rays are absorbed by the blue pigment, and the blue are absorbed by the yellow pigment; the result is that the rays which are reflected by both are seen, namely, the green ones. If, however, a yellow and a blue light from the spectrum are superimposed the effect is white. Mixtures of any two colours a certain distance apart in the spectrum produce white and these pairs of colours are called complementary colours. If colours farther apart are chosen one obtains extra-spectral colours such as purples, and if closer together a colour which lies in the spectrum between the two exciting colours. As first pointed out by Thomas Young, the simplest combination which can reproduce all the various coloured sensations is a mixture of three colours. He postulated, therefore, that there are three different end organs : one for red sensations, a second for green, and a third for violet sensations. On the other hand Hering was so impressed by the behaviour of complementary colours, that he enunciated a hypothesis that there are three substances which are either built up or broken down according to the colour of light to which they are exposed.

TABLE LIV  
HERING'S PAIRS OF COLOUR-RECEIVING SUBSTANCES

| <i>Substance.</i> |   |   |   |                          |   |                      | <i>Sensation produced.</i> |       |
|-------------------|---|---|---|--------------------------|---|----------------------|----------------------------|-------|
|                   |   |   |   | <i>By Decomposition.</i> |   | <i>By Synthesis.</i> |                            |       |
| Black-white       | . | . | . | .                        | . | .                    | White                      | Black |
| Red-green         | : | : | : | :                        | : | .                    | Red                        | Green |
| Yellow-blue       | . | . | . | .                        | . | .                    | Yellow                     | Blue  |

For instance, exposure of the retina to red light is supposed to cause decomposition of the red-green substance. On removing the red light and looking at a neutral colour the excess of decomposition products of red-green substance facilitates synthesis with the result that a green after-image results.

Many other hypotheses have been suggested as to the process of colour vision, but the two above mentioned will form the basis of the following discussion.

**Colour Contrast.** In the section on after-images (p. 410) it was stated that in negative after-images of coloured objects the colours are altered. In general the negatively coloured after-image presents the colour complementary to the original object. If a coloured diagram be looked at for 60 seconds by staring at a black dot in its centre and then a plain wall be looked at, the negative after-image will be seen.

According to Hering's hypothesis a green colour causes a building up of red-green substance. On looking at a neutral (grey) surface the excess is broken down, giving a red sensation. The reverse holds good on using a red surface for the initial exposure.

Parallel explanations hold for the yellow-blue and black-white substances. Equal degrees of red-green and yellow-blue stimulation cancel each other, leaving only the black-white component of the light, hence complementary colours produce varying degrees of grey.

According to Helmholtz, parts of the retina are fatigued by certain colours so that a neutral colour (grey) will cause a weaker sensation of the colour to which fatigue has been produced, and the grey appears, as the complementary colour. These negative after-images are often spoken of as the result of *successive contrast*.

If one places a grey strip on a coloured background and both pieces are covered by thin tissue paper the grey will appear as if tinged with the colour complementary to the background. According to Hering the colour (e.g. green) causes a change in equilibrium (building up of red-green substance), and the substance in excess diffuses into the neighbouring area producing the complementary sensation (breaking down of diffused red-green substance produces the red sensation). According to Helmholtz, a colour is dependent

largely on judgment, and when a grey strip is placed beside green, the grey is judged to be less green than it really is, i.e. it appears tinged with red. This is known as *simultaneous contrast*.

One great difficulty encountered in investigating this problem is that the central nervous system acts as a whole and attempts to compensate for any abnormal circumstances. For instance, if one looks through a stereoscope so that the image of a red penny stamp falls on one retina, and a green half-penny stamp on the corresponding area of the other retina, the nervous system is faced with the problem of a red and a green image from apparently the same object. Frequently the result is that one sensation is inhibited and this inhibition may vary so that first a red then a green stamp is seen. This is called *rivalry*. Sometimes, especially if one looks at the stamps for a longer time, the difficulty is solved in another way. The complementary colours could come from the same object if it were black and white, and the stamps sometimes fuse to give a steel-engraving effect. Thus we see that colour fusion may occur, even if the colours are presented to separate eyes, and that inhibition may occur and abolish a sensation although the retina is being stimulated.

In the same way a modification of Hering's experiment to show that colour contrast is retinal can be used to show that parts beyond the retina are also concerned.

If a stereoscope card is coloured half red and half blue, and on non-corresponding areas two grey strips are placed, a purple ground may be seen through the stereoscope (if rivalry does not obscure the fusion), and the two grey strips appear, one orange and the other blue-green. The strips are the complementary colour of their own background, and not that of the apparent background. This shows not only that the contrast is due to direct action on one retina, but also that the effect of the coloured background on the other retina has been inhibited because if it had not been thus inhibited the grey strip on the blue would have shown the complementary colour plus the red due to stimulation of the corresponding area of the opposite eye, and the grey strip on the red would have shown the complementary colour plus the blue. In view of these complications it is at present impossible to draw conclusions from experiments involving the correlation of visual sensations with physical stimuli.

**Photo-chemistry.** If light is to produce stimulation some of it must be absorbed, and the absorbed energy used to stimulate the retina. There is in the retina a coloured substance which absorbs and is bleached by light. This is a purple pigment, rhodopsin, seen in the outer limbs of the rods. It can be extracted by means of bile salts. The classical method used to show the action

of rhodopsin or visual purple is to expose the eye of an animal which has been in the dark to a bright object such as a window, immediately kill the animal and place the eye in alum. The alum fixes the unchanged visual purple so that the image of the window can be seen as bleached areas against a purple background. This effect is a most satisfactory photo-chemical mechanism to explain the action of light on the retina, but it does not explain how colours can be differentiated. If we are to understand colour vision in the same way, we must imagine that rhodopsin consists of several pigments or find some additional mechanism for colour analysis.

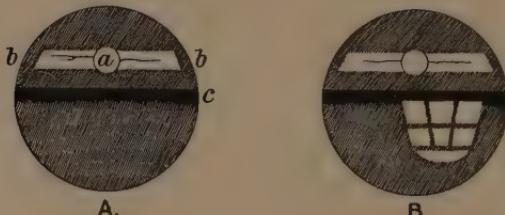


FIG. 217.—A, Normal Appearance of the Retina in the Rabbit's Eye before Exposure to Light. B, Optogram of a Window after Exposure of Eye (Kühne).

*a* = entrance of optic nerve, *bb* = a colourless layer of medullated nerve fibres, *c* = a layer of deeper colour separating the lighter upper from the more heavily pigmented lower portion.

filtered. For instance a red globule would pass through, but would stop green rays. Thus provided that the cone is sensitive to any wave length of visible light it will be differentially stimulated according to the colour of the cone globule. This is analogous to such systems of colour photography as Lumière or Paget processes, where a common sensitive film is altered as a fine mosaic according to the colour of the incident light, and the colour of the screen through which the light passes before it reaches the film.

**Alterations of the Retina Produced by Light.** In addition to bleaching of the visual purple there are well-recognized differences between the frog's eye when the frog has been kept in the dark and when it has been exposed to light.

TABLE LV

EFFECT OF LIGHT AND DARKNESS ON FROG'S EYE

|          | <i>Eye Dark-adapted.</i>                                | <i>Eye exposed to Light.</i>                               |
|----------|---|--|
| Pigment. | Retracted towards choroid.                              | Extended towards rods and cones.                           |
| Cones .  | Extended so as to be partially embedded in the pigment. | Retracted so as not to be entirely covered by the pigment. |
| Rods .   | Exposed to light.                                       | Partially screened from light.                             |

Such a mechanism is suggested by the coloured globules found in the cones of the retinae of birds, reptiles, and naked amphibians. At the junction of the cones with their bodies are minute coloured spheres, hence if the cone is the sensory receptor any light falling on it will be

These appearances suggest that in dim light the rods are well exposed, but that they are screened from strong illumination, and that the cones are always more or less exposed.

*Dark Adaptation and the Functions of the Rods and Cones.* If one remains in the dark for a prolonged period of time (from thirty minutes to two hours) the eyes become extremely sensitive to weak illumination. This increase in sensitivity is explained by the relations of rods and cones to the retinal pigment described in the preceding paragraph. The increase in sensitivity is more marked at the peripheral parts of the retina. In order to investigate the peripheral parts of the eye we use an instrument called a perimeter.

The *Perimeter* consists of a curved arm forming a quadrant of a circle. The arm is pivoted at one end so that by rotation it can trace out a hemisphere. There is an upright so arranged that the eye under observation is situated at the centre of the hemisphere, and a fixation point is on the axis round which the quadrant revolves. Whilst the observed person is looking at the fixation point the various parts of the retina can be investigated by coloured lights or objects attached to the rotating arm. The instrument is graduated along the quadrant in degrees, and the rotation of the quadrant can also be measured in degrees.

This instrument can be used to investigate the field of vision, and by it we determine how far from the fovea the retina is sensitive to light : the distances from the fixation point in degrees are plotted as equidistant concentric circles, and the axis in relation to the eye is plotted as degrees round the concentric circles. When such a chart is made for the normal eye an irregular figure is formed. The margins of this figure are due partly to projections from the face, e.g. the nose, blocking the path of the rays of light, and they consequently are not the limits of sensitivity of the retina.

Histologically it is found that the central part of the retina

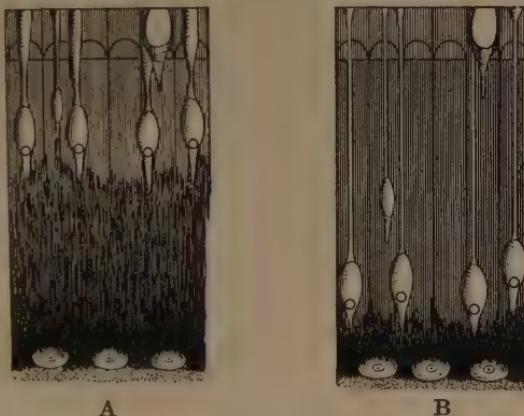


FIG. 218.—Section of Frog's Retina (after Englemann).

A = after exposure to light, B = after being kept in the dark. The direction of the light would be from the top of the figure towards the bottom.

contains many cones but that towards the peripheral parts of the retina the cones become few and far between. The rods are few in number near the fovea, but they greatly outnumber the cones towards the margins of the retina.

The dark-adapted eye is about 1,000 times more sensitive to light on its peripheral portions than the light-adapted eye, but the increase in sensitivity is less marked on the central portions.

The peripheral part of the retina is less sensitive to colours than the central part. With the perimeter an object or light may be visible, but if coloured, the colour may not be recognized.

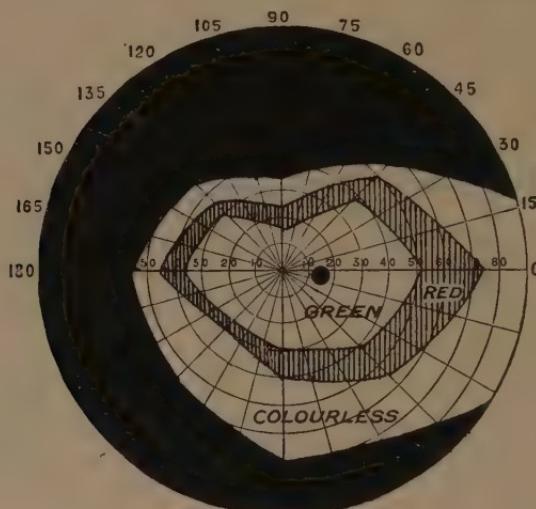


FIG. 219.—Field of View of Author's Right Eye for Coloured Pigments.

The outer (colourless) zone represents the area in which the object can be seen but its colour is not recognized. The outer margin of the shaded (red) area shows the limit where the colour of red papers was recognized. The inner margin of the shaded area shows how much farther the object must be moved before the green paper could be recognized as green.

The histological arrangement of rods and cones, the increased sensitivity of the peripheral parts of the retina to light, and the failure of colour recognition on the peripheral parts of the retina, suggest that the rods are organs which are stimulated by light irrespective of its colour, whilst the cones are organs for colour discrimination (von Kries).

If one looks at a spectrum of which the intensity is gradually reduced the colours fade and the most brilliant area shifts from the yellow towards the blue. This change can be shown in another way by two coloured windows, red and blue, of apparently equal brightness. If the intensity of the light is reduced the blue will appear brighter than the red (Purkinje phenomenon). This shift of the spectrum makes the maximum brightness correspond to the maximum absorption of light by rhodopsin.

There is much further experimental evidence that can be interpreted on the supposition that rods are used for perception of light and shade, whilst the cones are used for perception of colour. It must be noted that the rods contain rhodopsin whilst the cones do not. Edridge Green believes that rhodopsin diffuses from the rods to the cones and that the function of the rods is merely to furnish the rhodopsin.

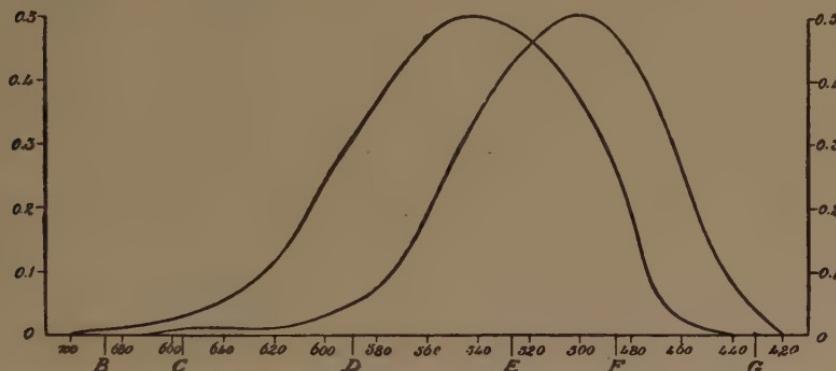


FIG. 220.—Absorption of Light of Different Wave Lengths by Visual Purple.

Curve to left with maximum about  $\lambda 540$  is for visual purple of fishes. The curve to the right with a maximum about  $\lambda 500$  is for that of mammals, birds and amphibia (from Rivers in Schafer's *Text-Book of Physiology*, Oxford Medical Publications).

**Hypochromatic Vision or Colour Blindness.** Certain persons differ from normal people in that they do not distinguish colours in the usual way. Thus colours which appear different to normal people appear the same to those with hypochromatic vision, a condition which is important both from the practical and theoretical aspects.

The practical point about this defect is that seamen, engine drivers, etc., depend on coloured lights for guidance at night. Now such individuals must recognize the colour without any means of comparison, hence they should be tested by a single colour at a time, and they must be able to state either its colour or its significance (i.e. danger signal, etc.). The simplest way to test this is by means of Edridge Green's colour lantern.

At one time coloured wools were used (Holmgren's Wools). The individual was given a skein of wool and asked to select wools to match it. The objection to this test is that the colour-blind person learns to judge by light and shade or other attributes of the wool, so that he may pass the test, yet still be incompetent to distinguish danger signals from other.

In addition to the colour lantern, Dr. Edridge Green has devised minor tests such as a bead test and a mosaic card test. He classifies people, according to the number of distinct colours that they can

recognize in the spectrum, into dichromics, trichromics, tetrachromics, pentachromics, and hexachromics, or those that recognize two, three, four, five, or six separate colours respectively. The normal person is hexachromic, although there are some who recognize seven distinct colours whom he calls heptachromics.

The explanation of the various forms of colour blindness depends upon the views one holds as to the mechanism for the recognition of colours. On the Young-Helmholtz hypothesis one can imagine for instance that an individual without receptors for red would fail to see the red element in natural objects and that the red end of the spectrum would be shortened. Such cases do occur, but there are others who fail to distinguish red yet are able to see the whole length of the spectrum.

If one assumes that colour-vision depends upon differential absorption of light, one can gain some insight into the possible causes of colour-blindness.

The amount of light transmitted through a coloured solution depends upon the concentration of the solution. If nerve endings are stimulated by differential absorption one may get varying results depending upon the concentration of absorbing material, and as the energy absorbed depends upon the absolute amount of light absorbed it is clear that for a wave length that is partially absorbed the stimulus will be greater if the intensity of light is increased.

As mentioned previously the simplest explanation of colour recognition is that, as in the retina of birds, reptiles, and naked amphibians, the human eye contains coloured screens which filter the light before it reaches the cones.

A red screen allows the corresponding cone to be stimulated by red light only. A yellow screen allows the corresponding cone to be stimulated by all rays beyond the blue of the spectrum, and an unscreened receptor would be stimulated by the whole of the spectrum. Light from the red end of the spectrum would stimulate all three types of receptor equally. Light from the green of the spectrum would stimulate the yellow-screened and unscreened receptors, but not the red-screened receptors. Light from the blue end of the spectrum would stimulate only the unscreened receptor. White light would stimulate all three receptors, but to different degrees, the red-screened least, the yellow-screened next, and the unscreened most. The unscreened receptors may be the rods as suggested above.

For this simple explanation only one photo-chemical substance is required, and rhodopsin may be that substance.

Absence of red-screened cones would cause failure to distinguish between all rays from the green to the extreme red end of the

spectrum, but there would be no shortening of the spectrum (deutanopia or photopic vision). Absorption of red rays by the media of the eye would cause shortening of the spectrum and decreased luminosity of red rays (protanopia or scotopic vision). Absence of red and yellow screens would lead to total colour-blindness in which the spectrum would appear in shades of one uniform colour.

Colour contrast may be due to the movements of the cones relative to the pigment of the retina. If red light is in excess the red-receiving cones may become embedded more than usual in pigment. On looking at a grey surface the red sensation will be relatively weak so that the grey will appear green.

In the case of simultaneous contrast it may be that the large area inducing the colour causes the pigment to shade some of the receptors for the area stimulated by the grey strip, with the result that the sensation corresponding to the complementary colour is produced. The effect of decided boundary lines in diminishing simultaneous contrast may be the result of limiting the spread of pigment migration in the neighbouring areas.

One must not overlook the fact that the image of a point is always a diffuse area with maxima and minima of light in concentric circles. These overlap and produce varying intensities of light. The effect of colour photography is due to this spread of light. A colour mosaic will produce overlapping of colours, hence the colour-screened cones will be stimulated by their appropriate rays and the result is a uniform picture. The diffraction of light is merely another method of producing colour fusion as the neighbouring colours of the mosaic overlap on the retina just as if the two colours were projected on the same screen.

Colour fusion may be produced :

- (1) By the simultaneous illumination of the retina—
  - (a) by two lights shining on the same surface;
  - (b) by overlapping of coloured diffraction circles on the retina from a mosaic of small coloured areas.
- (2) By successive illumination such as the rotating disc.
- (3) By illuminating corresponding parts of the two retinæ by the separate colours.

**Luminosity Measurements.** The brightness of a light is extremely difficult to measure. Comparisons are usually made between a standard light and the one to be tested. When different colours are concerned the luminosity is merely an expression of individual opinion.

An interesting method for measuring luminosities is by means of the rotating colour-mixer. If black and white sectors are revolved they produce a grey when the speed of rotation is sufficiently great to cause fusion. Short of the speed at which fusion

occurs the sensations rise and fall, producing an intermittent effect called "flicker." The rate at which the stimuli must follow each other in order to cause a uniform sensation, is a function of the brightness of light; hence the rate of revolution at which flicker is abolished can be used to measure luminosities.

The methods by which two lights can be compared are purely physical, although the judgment as to the matching of the lights depends upon the individual who makes the comparison.

**Nutrition of the Eye.** The maintenance of the eye involves several special points; the transparent media, for instance, do not contain blood-vessels, and they are nourished by a flow of lymph. The position of the various structures is maintained by the tension which exists inside the resisting sclerotic and cornea. Both these purposes are served by a flow of lymph from the ciliary processes (and possibly from the choroid coat), which passes thence, to be absorbed through the spaces of Fontana into the canal of Schlemm.

If the pressure in the eye becomes too great the condition is known as glaucoma. It is a serious menace to vision because the retinal blood-vessels may be obliterated by the pressure. The tension in the eye can be estimated by the hardness of the eye-ball. With the ophthalmoscope the retina will appear pale when the blood is squeezed out of the vessels.

The central connections of the optic nerve are shown in Fig. 221.

Each optic nerve can be divided, one half containing fibres from the temporal half of the retina, the other containing fibres from the nasal half. When the two optic nerves meet, approximately the inner half of each nerve crosses in the optic chiasma whilst the outer half remains on the same side. Each optic tract therefore contains fibres from the temporal half of the ipsilateral retina and from the nasal half of the contralateral retina.

By this arrangement the fibres from corresponding parts of the two retinae pass to the brain in the same tract. As the images are inverted on the retina the light rays from objects on the right side of the visual fields are focussed on the temporal half of the left retina and the nasal half of the right retina. The fibres from these two halves are collected in the left optic tract. Impulses from objects on the left side of the visual field ultimately reach the right optic tract. The reversal of images on the retina may be the factor which has caused the reversal of control by the cerebrum so that the left half of the cerebrum controls the movements of the right side of the body. The optic tracts pass dorsally and they are distributed to the pulvinars of the optic thalamus, the external geniculate bodies and the superior corpora quadrigemina. From these three stations the impulses are relayed to the occipital cortex. From the superior corpora quadrigemina fibres also pass

to the nuclei of the third, fourth, and sixth nerves for the control of reflex eye movements.

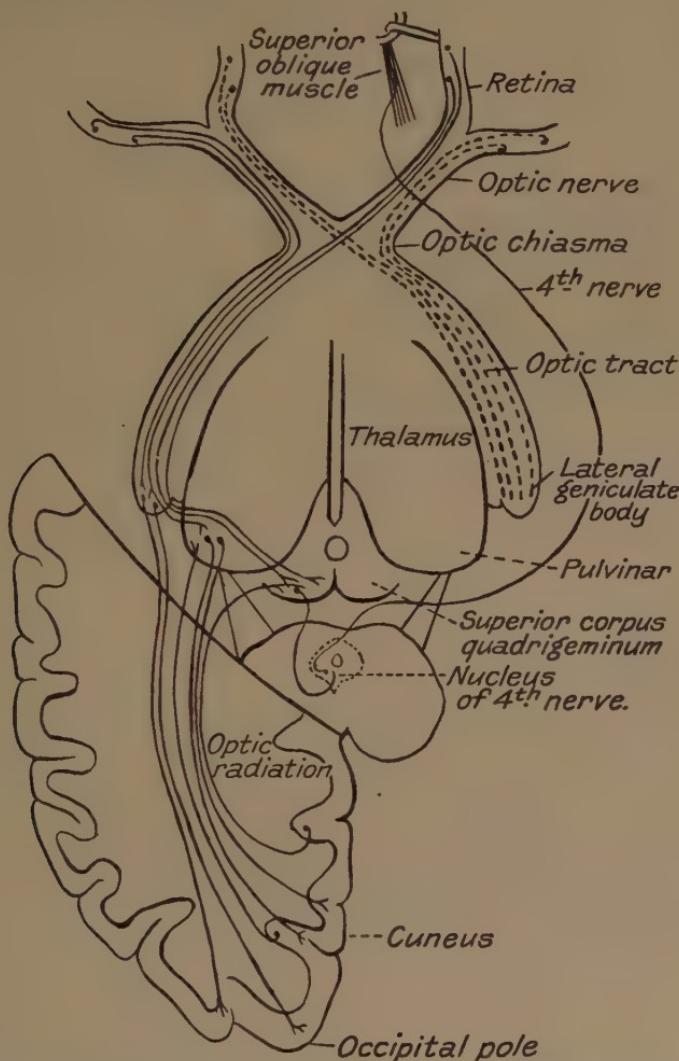


FIG. 221.—Diagram to show Connections of the Retinae with the Basal Nuclei and Cortex Cerebri (redrawn from Ranson).

The optic nerve contains some afferent fibres the function of which may be related to the movements of the retinal pigment and of the cones.

## CHAPTER XXXI

### SPEECH AND HEARING

Sound is produced by periodic alterations in air pressure. Like other stimuli which produce sensation we find that it can be analysed into an intensity factor or loudness, and a quality factor or tone. The direction from which a sound comes can also be recognized.

The loudness of a sound is dependent on the difference of pressure which is produced : the tone depends on the frequency of the changes in pressure. A pure note may be represented as a sine curve in which the height of the curve (pressure) represents the loudness and the number of waves per second represents tone. In the case of light the wave length is the unit of measurement, but in sound

it is the frequency of vibration ; these two are related by the equation : frequency = speed  $\div$  wave length.

The human ear can hear frequencies of from 16 to 40,000 per second. Many people cannot hear such a wide range as that, so these are extreme limits. Within



FIG. 222.—Examination of the Larynx by the Laryngoscope (Flack and Hill).

Above : mirror to be held at the back of the throat. *a* = annular mirror, *b* = light.

these limits the range of notes used in music forming the musical scale extends from about 30 to 4,000 vibrations per second.

#### Speech

Articulate speech is peculiar to the human species. For it we possess a special vibratory mechanism in the larynx. The essential part of the larynx consists of two stretched bands of connective tissue covered by a thin firm layer of stratified epithelium forming the vocal cords.

*Laryngoscope.* The larynx may be examined by means of the laryngoscope, which consists of a concave mirror pierced by a

central hole. This reflects light into the open mouth of the person being examined. A small mirror set at an angle on a long handle is held against the back of the throat, so that light is reflected down the larynx. The larynx is viewed through the central hole, and

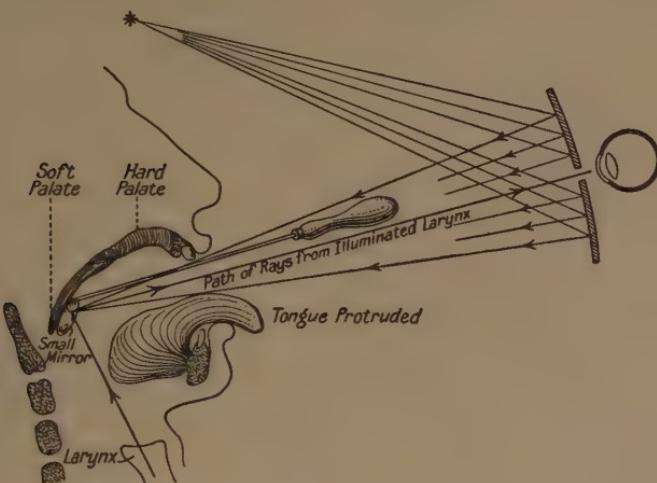


FIG. 223.—Diagram to show the Path of Light Rays when the Larynx is being Examined (Flack and Hill).

the reflection of the structures is seen in the small mirror at the back of the throat.

Figs. 224 and 226 show several different positions of the parts in the larynx. During respiration the vocal cords are abducted by the posterior crico-arytenoid muscles. These pull on the muscular processes of the arytenoid cartilages, rotating these cartilages on the cricoid cartilage. With forced inspiration the cords are in extreme abduction. The cords move inwards slightly during expiration. During phonation the cords are adducted partly by the lateral crico-arytenoid muscles, which antagonize the posterior cricoarytenoids, and partly by the arytenoid muscles, which pull the two arytenoid cartilages together.

The vocal cords are tightened by the crico-thyroid muscles. These pull the anterior part of the ring of the cricoid cartilage



FIG. 224.—View of Larynx obtained by the Laryngoscope.

*a*, epiglottis; *b*, thyroid; *c*, vocal cord; *d*, aryepiglottidean fold; *e*, cartilage of Wrisberg; *f*, cartilage of Santorini; *g*, pharynx.

towards the thyroid cartilage. Owing to the joint between the cricoid and thyroid cartilages the movement of the front of the ring towards the thyroid causes a movement of the top of the cricoid away from the ventral wall of the thyroid cartilage. In this way the cords, attached to the thyroid ventrally and the arytenoids dorsally, are stretched.

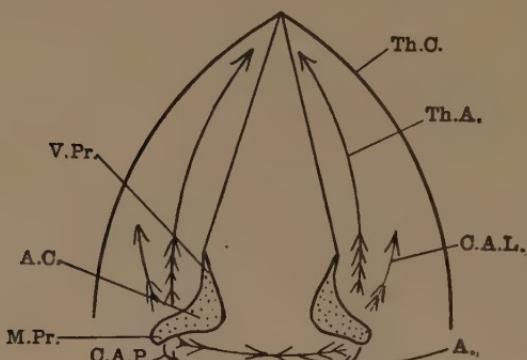


FIG. 225.—Scheme of Laryngeal Muscles  
(Parsons and Wright).

Th.C., thyroid cartilage; A.C., arytenoid cartilage; Th.A., thyro-arytenoideus; C.A.L., crico-arytenoideus lateralis; C.A.F., crico-arytenoideus posticus; A., arytenoid; V.Pr., vocal process of arytenoid; M.Pr., muscular process of arytenoid.

cords so that vibration may be limited to only part of their length.

The notes are produced by forcing air through the chink between the two cords. The cords vibrate just as a stretched wire does in a wind, or as does a blade of grass held stretched between the two

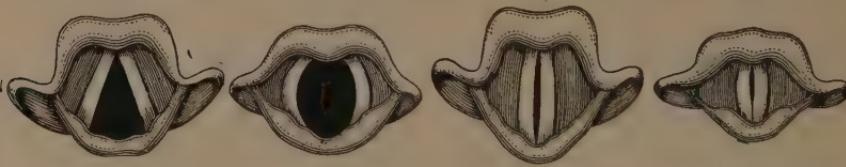


FIG. 226.—Diagrams to illustrate the Position of the Vocal Cords under Various Circumstances.

- (1) Position of rest. (The vocal cords are midway between abduction and adduction.)
- (2) Position during forced inspiration. (The vocal cords are in extreme abduction.)
- (3) Position during vocalization ("chest voice"). The vocal cords are adducted and vibrating in their entire length.
- (4) Position during vocalization (falsetto voice). The vocal cords are adducted and vibrating in their anterior portions only.

thumbs does when one blows strongly between the thumbs. The note produced depends on the length, tension, and mass per unit length of the cords. The formula for the note given by a vibrating

string is  $n = \frac{1}{2l} \sqrt{\frac{T}{m}}$  where  $n$  is the frequency,  $l$  = the length of the vibrating segment,  $T$  = the stretching force in dynes, and  $m$  =

the mass of one centimetre of the string in grams. Note, for instance, the difference in tone in the average male and female voices.

The tension of the cords can be varied as described above by the contractions of the muscles attached to the cartilages. When the whole cords are used, chest or deep notes of the normal register are produced. The thyro-arytenoids may limit the length of the cord which can vibrate. Under these circumstances the falsetto or high notes of the head register are sounded. Whispering is caused by speaking with the vocal cords abducted : hence the laryngeal note production is absent.

Vowel sounds are due to alterations in the shape of the mouth and upper air passages : thus resonance is caused for different notes.

*A* is produced by keeping the tongue moderately raised. The lips are retracted and opened to form an oval aperture. *E* sound is caused by raising the tongue from the *A* position to narrow the space between it and the hard palate. *I* is sounded by depressing the tongue from the *A* position to make a larger space between the tongue and hard palate. *O* is heard when the lips are pushed forward from the *I* position of the lips to form a small round opening. *U* is obtained from the *O* position by protruding the lips further to form a longer narrow opening, and by raising the back of the tongue towards the palate.

The consonants are caused by interruptions of the air current either in the form of an explosive commencement or rhythmical variations as in a trilled *R*. They can be classified by the part of the mouth which produces the interruptions and whether they are explosive or vibrative consonants.

#### CONSONANTS

| Type.                     |   |   | Explosive. | Vibrative.                     |
|---------------------------|---|---|------------|--------------------------------|
| Labials                   | : | : | B, P       | M, W                           |
| Labio-dentals             | : | : | V.         | F,                             |
| Linguo-dentals            | : | : |            | Th, S, Z, Sh, Zd               |
| Anterior linguo-palatals  | : | : | T, D       | C, J, L, N, R (trilled)        |
| Posterior linguo-palatals | : | : |            | G, H, K, Q, R (guttural), X, Y |

By articulate speech very complicated pressure waves are produced, and it is one function of the ear to resolve these pressure waves into sensations of sound.

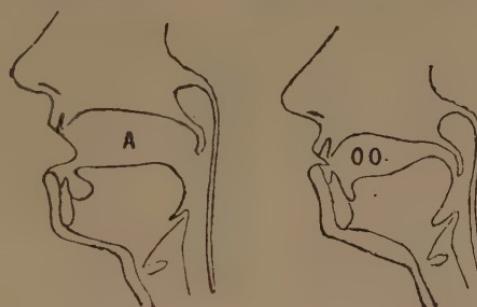


FIG. 227.—Shape of the Mouth in sounding Two Different Vowels (L. Hill).

### The External and Middle Ear

**Structure.** The ear is divided into three parts external, middle and internal. *The External Ear* consists of the pinna and of the external auditory meatus. The pinna, in some animals at least, collects sound waves and reflects them into the external auditory meatus. By movements of the ears variation in loudness can be produced, and in that way the direction of sound may be judged. The external auditory meatus consists of a tunnel surrounded by cartilage and bone; the lining of it consists of stratified epithelium. In the epithelium are found certain modified sebaceous glands called ceruminous glands which secrete a bitter wax. The inner end of the external auditory meatus is closed by the tympanic membrane, which is placed at an angle of  $55^{\circ}$  to the canal, sloping downwards and inwards. It is pulled inwards asymmetrically by the attachment of the handle of the malleus to a point slightly below the centre of the membrane. This asymmetrical attachment



FIG. 228.—Method of Examination of the Ear-Drum by Reflected Light (Flack and Hill).



FIG. 229.—View of Tympanic Membrane (Flack and Hill).

forms the membrane into a deformed funnel, the apex of which is called the *umbo*.

The condition of the external auditory meatus and the tympanic membrane may be examined by means of a reflected light and pierced mirror similar to that of the ophthalmoscope. A conical tube or speculum is used to straighten out the slightly curved external auditory meatus.

*The Middle Ear* or tympanum consists of a cavity in the petrous portion of the temporal bone. The outer wall is formed mainly by the tympanic membrane. The inner wall contains two openings closed by membrane. The first, opposite to the tympanic membrane, is the *fenestra ovalis*; the second, below and behind the *fenestra ovalis*, is the *fenestra rotunda*. Between these two is seen the *promontory* formed by the projection outwards of the lower turn of the cochlea.

The posterior wall has openings communicating with the mastoid cells. The anterior wall has an opening for the eustachian tube, a bony and cartilaginous canal by which the tympanum communicates with the throat, terminating on the side of the pharynx above the soft palate. The tympanum is bridged by a chain of small bones called the ossicles. These are three in number, the malleus, incus, and stapes. The malleus consists of a head and three processes—the manubrium, which extends downwards and by its extremity pulls the tympanic membrane inwards to form the asymmetrical cone mentioned above; the processus gracilis, a long delicate process which passes outwards and forwards, to be attached to the Glaserian fissure above the tympanic membrane; and the processus brevis, a small conical projection to which is attached the tendon of the tensor tympani.

The incus consists of a quadrilateral body with two processes: the processus brevis which is directed backwards, and is attached to the margin of the opening of the mastoid cells; and the processus longus, extending downwards and ending in a rounded projection which forms in the foetus a separate bone, the os orbiculare. The malleus and incus form a compound lever. They are united by the head of the malleus articulating with the body of the incus. They rotate round an axis formed by the processus gracilis of the malleus and the processus brevis of the incus. Thus movement of the manubrium inwards causes movement of the processus longus of the incus inwards, whilst the head of the malleus and body of the incus move outwards.

The long process of the incus articulates with the head of the stapes. The crura of the stapes diverge from the neck, through which they are attached to the head, to the base or foot-plate of the stirrup. The base is attached by ligaments to the margin of the fenestra ovalis. The stapes is thus swung horizontally between the processus longus of the incus and fenestra ovalis.

Two muscles are attached to the chain of ossicles. The first

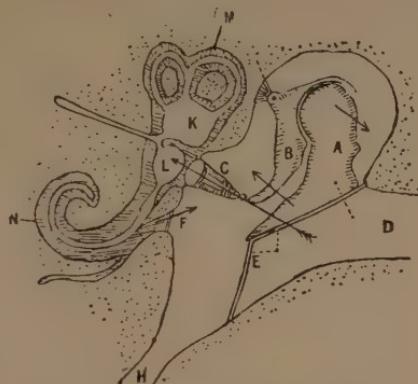


FIG. 230.—Diagram of Ear, showing Ossicles (Leonard Hill).

A = malleus, B = incus, C = stapes, D = external auditory meatus, E = tympanic membrane, F = foramen rotundum, H = eustachian tube, K = utricle, L = saccule, M = semicircular canals, N = cochlea. The shaded part shows the perilymph in the bony labyrinth; the white part is the membranous labyrinth containing endolymph.

arises in a canal alongside of the eustachian tube and its tendon passes over a projection of the bone separating the canal from the eustachian tube. Thus the muscle runs backwards, but the tendon turns almost at right-angles to pass outwards to be inserted into the processus brevis of the malleus. By the contraction of this muscle the handle of the malleus is pulled inwards, thus stretching the tympanic membrane : hence it is called the tensor tympani. The second muscle arises inside a bony projection on the inner wall of the tympanum called the pyramid. The tendon of the muscle passes out through a small opening at the apex of the pyramid and passes forwards to be inserted into the neck of the stapes. By the contraction of the stapedius the stapes is twisted so that the back part of the foot-plate is pressed inwards, and the front part is pulled outwards. This tightens the ligaments which hold the foot-plate of the stapes to the margin of the fenestra ovalis, thus limiting any to-and-fro movement of the stapes.

**Function.** As mentioned previously pressure-waves reaching the pinna are reflected into the external auditory meatus. The importance of reflection of waves can be shown by placing one's hand in the form of a shallow saucer behind one's ear when listening to an almost inaudible sound. The pressure waves reach the tympanic membrane and alternately press it inwards and suck it outwards. If the tympanic membrane were symmetrical it would resonate to special notes, but owing to the asymmetrical attachment of the handle of the malleus, it is efficient over a wide range of frequencies. In order that the maximum effect be produced, it is essential that the tympanic membrane should not be stretched unduly ; the pressure, therefore, in the tympanum should be equal to that of the surrounding atmosphere : hence the communication of the tympanum with the pharynx through the eustachian tube.

Any movement of the tympanic membrane will cause corresponding movements of the handle of the malleus and the long process of the incus. This will cause movements of the stapes so that the foot-plate will press against and pull from the fenestra ovalis as the tympanic membrane moves inwards or outwards respectively. The mechanical advantage of the chain of ossicles is that they magnify the pressure differences, and the two muscles modify the transmitted pressure differences. As the lip of the handle of the malleus is one and a half times as far from the axis of rotation as is the os orbiculare, the force of the movement will be increased one and a half times, and the amplitude will be reduced by two-thirds.

The area of the tympanic membrane is 71 sq. mm., whilst that of the fenestra ovalis is 3 sq. mm., which gives a ratio of about one to twenty-four. The pressure, therefore, on the smaller membrane

will be twenty-four times that on the larger. This with the additional pressure magnification due to the leverage action of the bones gives a total magnification of thirty-six. (If, as has been suggested by Keith, the foot-plate of the stapes is hinged so that the effective stroke of its piston-like foot-plate against the fenestra ovalis is halved, we get the available pressure doubled again, giving a total magnification of seventy-two times).

Thus we see that the chain of ossicles convert the slight pressure differences of sound waves into something more effective in producing pressure against the fenestra ovalis. The tensor tympani and stapedius are used to modify the mechanical conditions so that faint sounds are more readily heard and loud sounds reduced in intensity. They do this by varying the tension of the tympanic membrane, and by limiting the excursions of the foot-plate of the stapes by tilting it in the fenestra ovalis. The articulation between the malleus and incus may act as a safety valve when excessively loud sounds reach the ear because it has been described as a ratchet arrangement which can slip and thus prevent injury to the internal ear.

The ratchet is arranged so that it can slip when the handle of the malleus is moved violently outwards.

### The Internal Ear

**Structure.** Although the internal ear has other functions than that of converting pressure waves into nerve impulses, it is better to describe the general structure of the internal ear, and leave to the next chapter the minute structure and the function of those parts not concerned with hearing.

The internal ear consists of a complex cavity, the labyrinth, in the petrous portion of the temporal bone. The central portion of the cavity is known as the vestibule. The vestibule has on its outer wall the membrane which closes the fenestra ovalis, and on its inner wall a series of perforations, macula cribrosa, for the passage of filaments of the auditory nerve. In front there is a coiled cavity like a snail-shell called the cochlea. Behind and above are five openings which are the ends of three curved canals—the semi-circular canals; there are only five openings instead of six, as two of the canals have one opening in common. As shown in Fig. 244 the semicircular canals are horizontal, anterior vertical and posterior vertical; one end of each is enlarged to form an ampulla, where it enters the vestibule.

The horizontal canal extends from the outer and back region of the vestibule to the upper and outer angle where the ampulla is situated. The posterior canal extends from the lower and back part of the vestibule, where the ampulla is situated, to the back

part of the vestibule, where it joins with the superior canal to open into the vestibule by a common entrance. The anterior canal has its outer end with the ampulla at the upper surface of the vestibule and its inner end joins with the posterior canal as already described.

Contained within the bony cavity is a *membranous labyrinth*. This is supported in liquid known as perilymph and contains a liquid known as endolymph. The parts of the membranous labyrinth correspond roughly with the bony labyrinth. Thus there are three membranous semi-circular canals and a canal of the cochlea, but the vestibule contains two membranous sacs, the utricle and saccule. The three semicircular canals open into the utricle and the scala media of the cochlea opens into the saccule. The utricle

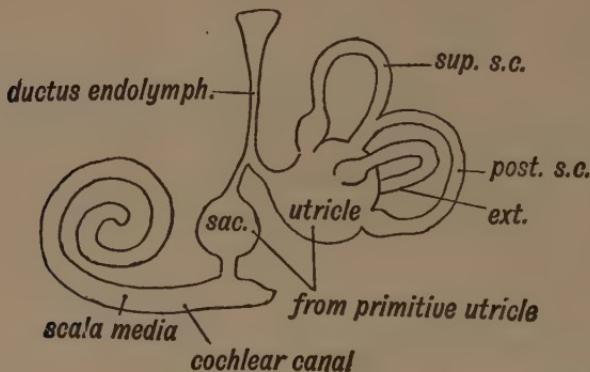


FIG. 231.—Diagram of Membranous Labyrinth (Keith).

and saccule communicate by a Y-shaped junction, the *ductus endolymphaticus*.

The semicircular canals, utricle and saccule will be dealt with in the next chapter, but we must now consider the cochlea as the organ of hearing.

**The Cochlea** in man consists of a spiral cavity in the petrous portion of the temporal bone which makes two and a half revolutions round a central core or modiolus. Projecting into the spiral canal from the modiolus is a delicate bony shelf, the lamina spiralis, from which extend two membranes—one delicate and slack—the membrane of Reissner—extending to the opposite wall at an angle of about  $30^\circ$ ; the other strong and taut—the basilar membrane, which forms a continuation of the bony shelf to the opposite wall of the canal. These two membranes divide the cochlea into three canals called the scala vestibuli, scala tympani and scala media. The first communicates with the vestibule, and the second terminates at the fenestra rotunda, being separated from the tympanum by a membrane. The scala media communicates with the saccule

and differs from the other two in that it contains endolymph, whilst they contain perilymph. At the end of the cochlea distal from the vestibule the scala media is absent, and the scala vestibuli and scala tympani communicate by an opening called the helicotrema. If uncoiled the cochlea would be represented as one tube inside another. The scala vestibuli and scala tympani are separated by the scala media, but they communicate through the helicotrema.

The *basilar membrane* has the following structure. Attached to the lamina spiralis is a homogeneous part consisting of material which resembles elastic tissue, the subarcuate zone. About one-third of the way across, the homogeneous material is united to striated fibrous-looking material called the pectinate zone. The outer edge of the membrane is attached to a conical mass called the ligamentum spiralis. The basilar membrane increases in width as it extends up the cochlea, being 0.21 mm. wide at the base of the cochlea, and 0.36 mm. wide at the apex.

*The Organ of Corti.* On the basilar membrane is a complex structure known as the organ of Corti. This consists of certain structures known as rods of Corti, against which are masses of epithelial cells, and above these is a massive structure known as the *membrana tectoria*. The rods of Corti form a double row with a tunnel between them. The inner rods rest on the lamina spiralis by an enlarged extremity and extend upwards and outwards to meet the outer rods. The latter extend downwards and outwards from the inner rods to the basilar membrane, where they are attached at the junction of subarcuate and pectinate zones of the basilar membrane.

The outer and inner rods join so that each inner rod lies between two outer rods and a large area of contact is present. The outer rod presents a swan-neck appearance : the inner rod somewhat resembles the ulna.

*The Fenestrated Membrane.* Resting against the rods of Corti

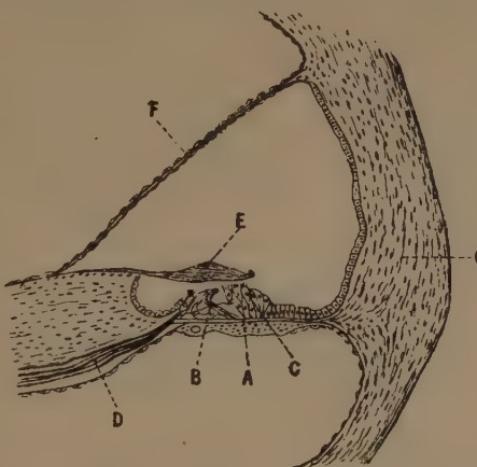


FIG. 232.—Section (Low Power) through Part of Cochlea, showing Membranous Canal of the Cochlea (after Retzius).

A, basilar membrane; B, rods of Corti; C, hair cells; D, fibres of auditory nerve; E, tectorial membrane; F, membrane separating off membranous canal of cochlea; G, wall of cochlea.

are certain large epithelial cells with hair-like projections. Between these cells and against their outer border are certain supporting cells. Covering the surface of these cells is a dense layer of elastic tissue with openings through which protrude the hair-like projections of the hair cells. It appears as if this fenestrated membrane held the tops of the cells rigid so that no movement of the cells relative to each other can take place.

In the modiolus are numerous nerve cells forming the ganglion spiralis of the auditory nerve. The fibres from these cells run outwards in the lamina spiralis to reach the hair cells. There is a single row of hair cells against the inner rods of Corti, and three or four rows against the outer rods.

The *membrana tectoria*, which lies above the fenestrated membrane, consists of a fusiform mass of elastic tissue united to the

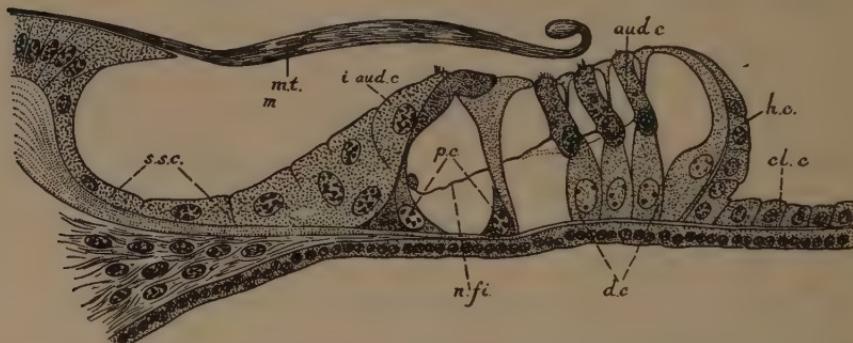


FIG. 233.—Section of Organ of Corti of a young Guinea-pig (redrawn from Dahlgren and Kepner).

*cl.c.*, cells of Claudius; *h.c.*, Hensen's cells; *d.c.*, Deitlers', or supporting cells; *aud.c.*, auditory, or hair cells (outer); *p.c.*, outer and inner pillar cells; *i. aud. c.*, inner auditory or hair cells; *n.fi.*, nerve fibres; *m.t.*, membrana tectoria; *s.s.c.*, cells lining sulcus spiralis.

lamina spiralis by a bony crest above the junction of the basilar membrane with the lamina spiralis. Its outer end is usually seen with a remnant of membrane attached to it which is generally stated to bind it to the rest of the organ of Corti, but it is usually torn away in the process of fixation and preparation of the section.

Stimulation of the nerve fibres is believed to result from the movement of the hair cells relative to the membrana tectoria.

At one time it was thought that the hair cells bumped against the membrana tectoria, but it is now believed that the hairs are bent or rubbed by a transverse motion of them across the membrana tectoria.

#### Analysis of Sounds

Unless we deny any analytical function to the ear we must endeavour to explain how various sounds can be recognized. So

far as we know there are no specialized structures in the brain for the analysis of sound, therefore we ought not to postulate them until we have proved that the peripheral organ cannot carry out the analysis.

There are two ways in which the cochlea might perform the analysis, either by some form of resonating mechanism or by a sound pattern, the possibility of a telephone-like conveyance to the brain and analysis there being, as pointed out above, a confession of failure to explain the function of the cochlea.

The first view is associated with the name of Helmholtz, and it is based on the fact that many structures can be so tuned that they vibrate selectively to rates of vibrations corresponding to those to which they are tuned. This hypothesis requires the basilar membrane to vibrate transversely in different regions for different notes. There is a certain amount of evidence in favour of this hypothesis, namely that the structures show a progressive change in size along the length of the cochlea. Deafness to high notes produced in workers, who continuously hear loud ringing noises, is associated with degeneration of the structures at the base of the cochlea (boilermaker's disease).

The second view is associated with the name of Waller and Ewald. It is based on the patterns produced by Chladni's plates. Thus the recognition of a note depends on the distance apart and amplitudes of the crests and troughs of the wave pattern produced on the basilar membrane.

Whilst both the above methods of interpretation are possible a study of the mechanical arrangements in the cochlea suggest that another mode of analysis may be the true explanation.

When a pressure wave reaches the fenestra ovalis the stapes presses against an almost incompressible fluid contained in a case rigid except for the membrane closing the fenestra rotunda. If it were not for this membrane the pressure in the whole cavity would rise simultaneously, and it is difficult to see how the pressure could be recognized. (A manometric recorder is however possible.) By the yielding of the membrane of the fenestra rotunda a mass movement of liquid results and this causes the stimulation of the nerve endings. The movement of liquid can occur through the helicotrema or owing to the difference of pressure in the *scalæ vestibuli* and *tympani* by the yielding of the basilar membrane. These two movements of liquid can be understood by reference to the Fig. 234. In order to understand the analysis of sounds we must first consider the basilar membrane.

**The Function of the Basilar Membrane.** The proximal end of the basilar membrane is narrower than the distal end (0·21 : 0·36), therefore a greater pressure is required to stretch it. Further,

the inner portion of the membrane is composed of elastic tissue and its junction to the outer wall of the cochlea is such as to give a suggestion of greater strength at the proximal end ; it may therefore be stretched at a greater tension. The structure of the organ of Corti also suggests that a greater force would be required to produce movement at the proximal end of the cochlea. The greater width of the basilar membrane at the distal end would cause a greater force for the same pressure per unit area, so that all these factors co-operate to produce a movement of the distal portion of the cochlea with a much smaller difference of pressure on the two sides of the basilar membrane.



FIG. 234.—Diagram of Internal Ear.

*SC* = semicircular canal, *A* = ampulla, *U* = utricle, *S* = saccule, *DE* = ductus endolymphaticus, *C* = cochlea, *SV* = scala vestibuli, *ST* = scala tympani, *SM* = scala media, *FO* = fenestra ovalis, and *FR* = fenestra rotunda.

will cause pressure differences along the basilar membrane. There will not be sufficient difference in pressure across the proximal part of the membrane to cause it to move, but somewhere further up the pressure will cause movement of the basilar membrane.

Once movement of the basilar membrane is produced the nerve endings will be stimulated by movement of the hair cells relatively to the tectorial membrane so that the hair cells are either tapped (Helmholtz), bent (Wrightson), or pulled (Hartridge).

In considering this mechanism one must remember that the vibration will be spread over a certain length of the membrane with a maximum movement near the centre of the strip. This has been well dealt with by Gray, who shows on the analogy of the sense

When pressure is applied to the fenestra ovalis the maximum difference in pressure is between it and the membrane closing the fenestra rotunda. The difference in pressure across the parts of the basilar membrane will diminish towards the helicotrema. This decrease will depend on two factors, the inertia and the viscosity of the liquid in the scalæ. With high notes the rapid changes in pressure will not be able to set the whole mass of liquid in motion, thus most of the difference in pressure will be across the more rigid part of the basilar membrane, and this part may be set in motion. With low notes of the same maximum-pressure difference, there will be more time for the liquid to be set in movement, hence before the membrane yields the perilymph will be set in motion and the viscosity of the liquid

of touch that the sensation produced is not that of the whole area affected, but of the point of maximum deformation.

Thus one concludes that the cochlea acts as an analytical mechanism for pressure waves and that there are sufficient variable factors to account for the analysis. Further there are enough separate nerve fibres for each one to carry a single impulse for a separate

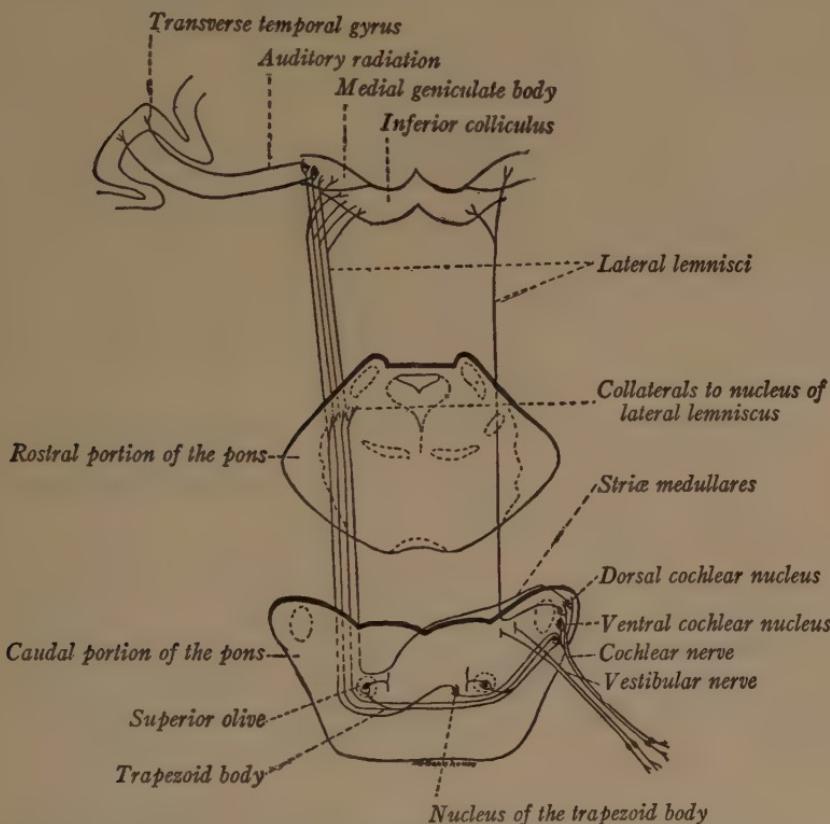


FIG. 235.—Diagram of the Auditory Pathway (based on the researches of Cajal and Kreidl).

note and therefore there is no need to postulate different types of impulses travelling up the same nerve.

The cochlear branch of the auditory nerve consists of fibres which pass from cells in the spiral ganglion in the modiolus of the cochlea. The peripheral fibres pass through the lamina spiralis to the organ of Corti, where they ramify in relation to the hair cells. The central fibres pass through the internal auditory meatus to the medulla.

In the medulla the fibres end in relation to two nuclei, one on the

dorso-lateral, and the other on the ventro-lateral surface of the restiform body. These are called the dorsal and ventral cochlear nuclei respectively. From the ventral cochlear nuclei relay fibres carry on the path by passing inwards to cross the mid-plane of the medulla. These transverse fibres form the trapezoid body. On reaching the lateral border of the opposite superior olivary nucleus the fibres turn in the cephalic direction, forming the lateral lemniscus (see p. 357). A few of the fibres from the ventral cochlear nucleus end in the superior olivary nuclei and others end in the nuclei of the trapezoid body.

From the dorsal cochlear nuclei, fibres pass dorsally and inwards, crossing the floor of the fourth ventricle as the *striæ acusticæ*. After decussating at the mid-plane they enter the reticular formation and join the lateral lemniscus of the opposite side. The lateral lemniscus ends at the inferior colliculus and the medial geniculate body; the latter sends a second relay of fibres by the auditory radiation to the auditory area of the cortex. The medial geniculate body is thus a relay station on the path of auditory sensations. The inferior colliculus is probably a reflex centre for sound.

**Conditioned Reflexes** (Pawlow). An interesting method for studying the analytical mechanisms of the special senses in animals is by means of conditioned reflexes. An example of such a reflex is as follows. A dog with a salivary fistula is fed and at the same time a tuning fork is sounded. After a period of training it will be found that the sound of a tuning fork will provoke a secretion of saliva: an association has been formed between the sound and the act of feeding. By using tuning forks of different frequencies and giving food only when a certain one is sounded the salivary gland will secrete only when that one is vibrating. It is possible in this way to test the analytical mechanism of the dog's auditory apparatus and to learn to what extent it can distinguish between closely-related frequencies. Similar experiments can be carried out using visual or other stimuli, and the method is a valuable one for studying the discriminating power of the various sensory mechanisms. The amount of saliva secreted is a measure of the intensity of the response.

By combining the conditioned stimulus with some other form of stimulus, not accompanied by the unconditioned (feeding) stimulus, the conditioned reflex may be inhibited. Repeated inhibition of a conditioned reflex causes the animal to become drowsy and to go to sleep. Inhibition, sleep and hypnosis are probably related states. A great deal of education is due to the development of conditioned reflexes and the associations of a stimulus affect the whole nervous system. The influence of conditioned reflexes forms the subject of Chapter XXXIX.

## CHAPTER XXXII

### INTEGRATION OF REFLEXES AND EQUILIBRIUM

In Chapter XXIII the phenomena of reflex action were described, but now we must study the way in which reflex action is regulated.

The first outstanding feature of reflex action is that it represents an harmonious whole. The ease and smoothness of movement of

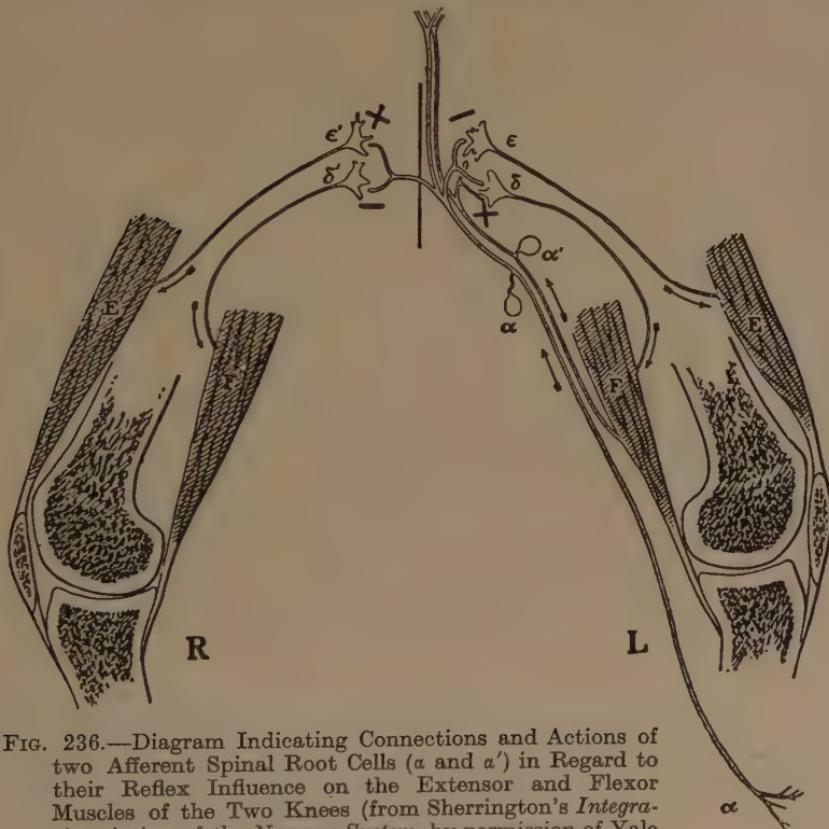


FIG. 236.—Diagram Indicating Connections and Actions of two Afferent Spinal Root Cells ( $\alpha$  and  $\alpha'$ ) in Regard to their Reflex Influence on the Extensor and Flexor Muscles of the Two Knees (from Sherrington's *Integrative Action of the Nervous System*, by permission of Yale University Press and Messrs. Constable & Co., Ltd.).

$\alpha$  = afferent fibre from skin below knee,  $\alpha'$  = afferent fibre from flexor muscle of knee,  $\epsilon$  and  $\epsilon'$  = efferent neurons to extensor muscles of the right and left knees,  $\delta$  and  $\delta'$  = efferent neurons to flexor muscles, E and E' = extensor muscles, F and F' = flexor muscles. The sign + indicates that at the synapse which it marks the afferent fibre ( $\alpha$  and  $\alpha'$ ) excites the motor neuron to discharging activity, the sign - indicates that at that synapse the afferent fibre  $\alpha$  (and  $\alpha'$ ) inhibits the discharging activity of the motor neurons. The effect of strychnine and tetanus toxin is to convert - into +.

a limb is due to the fact that when one group of muscles pulls on it the muscles which produce the opposite effect relax. Thus by isolating in a decerebrate cat the extensor muscle, and also the flexor muscle of the knee, it is found that stimulation of the contralateral great sciatic nerve causes contraction of the extensor and relaxation of the flexor muscles, whilst stimulation of the ipsilateral sciatic

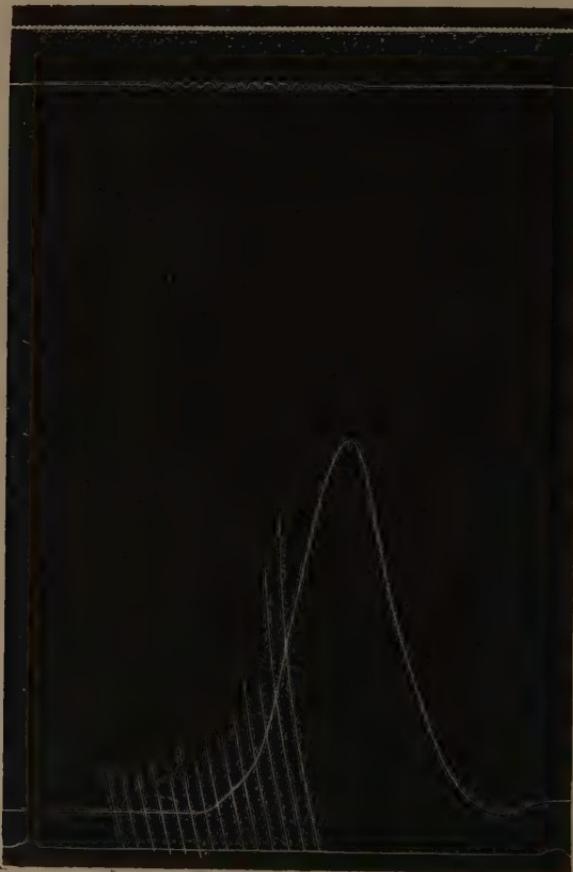


FIG. 237 (A)

causes relaxation of the extensor and contraction of the flexor. This reciprocal action is described as the reciprocal innervation of antagonistic muscles.

In order to show the relaxation of muscles it is necessary that there must be a certain amount of contraction already existing in the muscles. This contraction is present in normal individuals, as shown by the fact that if a tendon is severed it is drawn apart by the shortening of the muscle, and by the slight amount of resistance



FIG. 237 (B)

FIG. 237.—A and B. The Flexion-reflex observed as (A) a Reflex Contraction of the Flexor Muscle of the Knee and (B) as Reflex Relaxation of the Extensor Muscle of the Knee (from Sherrington's *Integrative Action of the Nervous System*, by permission of Yale University Press and Messrs. Constable & Co., Ltd.).

The intensity of the stimulating shocks was feeble, hence the relatively long latent period and the number of stimuli sent in before the response occurred. Time marking in 1/100 secs. at top and in secs. at bottom.

to passive movement of the limbs which disappears in complete unconsciousness such as sound sleep and deep anaesthesia. This slight degree of contraction is known as tone of the muscle. The relaxation in a reflex is therefore a decrease in contraction and is called inhibition.

There are two forms of preparation which are used in studying reflexes, in both of which the complicating effects of the cerebrum are got rid of. The first of these consists in cutting the spinal cord. If the cut is caudal to the exit of the phrenic nerves respiration may continue and the reflexes can be studied over a long period of time. If the cut is made cephalic to the exit of the phrenic nerve artificial respiration must be used, and the experiment is usually of short duration. The decapitated cat is a useful preparation, as the animal is killed by removal of its head, after which anaesthesia is not required and the carcase of the animal will show good reflexes. The immediate effect of cutting the cord is traumatic shock, in which the reflexes are depressed or absent, but after this stage has passed the reflexes are well marked, and they can be produced with almost mechanical regularity.

The second form of preparation consists of removal of the cerebrum, including the basal ganglia. This preparation soon passes into a condition in which its limbs are stiffly stretched out, a condition known as decerebrate rigidity.

The "spinal" preparation is used to study rhythmical reflexes, whilst the "decerebrate" one is more useful in studying conditions of muscle tone; both are concerned in reflex actions.

Before we can understand the reflex actions we must know something about the postural condition known as decerebrate rigidity. This is governed by impulses associated with the brain stem and the internal ear, which will be studied later in this chapter.

**Reflex Tone.** The decerebrate rigidity depends upon reflex afferent impulses because it disappears if the dorsal roots are cut. Further the rigidity can be affected by impulses from the muscle itself. If a muscle, e.g. the deltoid, which has a multiple nerve supply is used the following experiment can be performed. Cut one of the branches close to the muscle so that stimulation of the central part can no longer cause contraction by direct conduction to the muscle. Then stimulate the central end preferably by a mechanical stimulation such as tying a ligature round it. The result is a relaxation of the deltoid showing that an afferent impulse has passed up to the cord and caused an inhibition of the contraction already existent in the muscle (Sherrington). The afferent fibres which produce this effect must come from the muscle, and we find there endings of a special sort. These consist of modified muscle fibres surrounded by ramifications of nerve endings, the

whole forming what is called a muscle spindle. The inference to be drawn is that tension or pressure in a muscle has something to do reflexly with the degree of maintained contraction existing in the muscle.

Sherrington has shown that there are apparently two types of muscle ending, one which produces inhibition of the muscles which act synergically with the muscle in which it is contained, and contraction of the opposing muscle groups; the other produces contraction of the muscle in which the ending is contained. The latter is preferentially stimulated by the slow alterations of potential produced by a rotating rheonome.

The limbs of a decerebrate animal tend to remain in the position

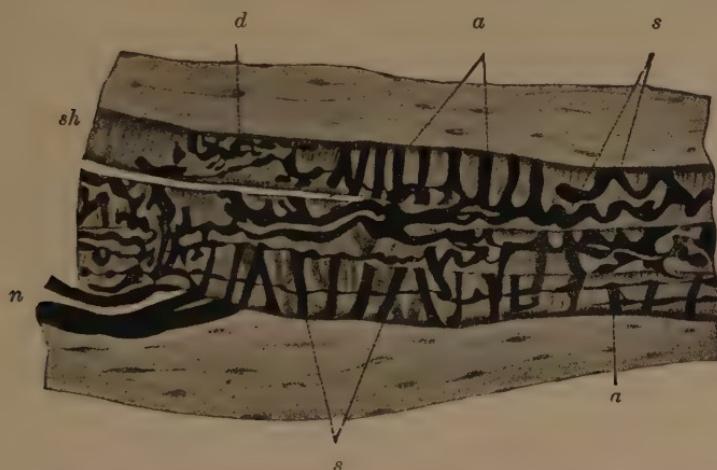


FIG. 238.—Nerve-endings in a Muscle Spindle (Ruffini from *Quain's Anatomy*).

*n* = nerve-fibres to spindle, *a* = annular endings of axon, *s* = spiral endings, *d* = dendritic endings, *sh* = connective-tissue sheath of spindle.

in which they are placed. Thus if the vasto-cruneus muscle is isolated in a decerebrate cat it is found that if the leg is extended it remains more or less extended, whilst if it is flexed it remains flexed, but with a tendency gradually to extend to its original position of decerebrate rigidity. This postural condition is compared to a ratchet in which the position is maintained until a movement causes the ratchet to catch in another position. The basis for this analogy is that decerebrate rigidity differs from a muscle contraction in that the energy expenditure during rigidity is not appreciably greater than during relaxed states of the muscles, whilst contraction causes a marked increase in oxidation (Roaf).

One of the factors in the maintenance of the rigidity are the muscle spindles and their afferent nerves, but there may be other

afferent impulses from tendons and joints which help to regulate the rigidity. The special nerve endings in tendons consist of axis cylinders without myelin sheaths. These form terminal arborizations with irregular varicosities on the network. Whether the afferent fibres from the skin help to regulate the position of the limbs is not known, but entire removal of the skin does not abolish the condition of decerebrate rigidity.

The presence of these afferent fibres which produce inhibition of the muscle from which they arise must have an influence on rhythmical reflexes. As pointed out above, the result of reciprocal innervation is that these same afferent impulses, in addition to producing inhibition of the muscle from which they arise, also cause contraction of the opposing muscle.

These afferent impulses which do not produce definite sensations are of use in informing us of the position of our limbs and they



FIG. 239.—Nerve-endings, Golgi Organ, in Tendon of Rabbit (Flack and Hill, redrawn from Dahlgren and Kepner after Hübner and De Witt).

are used when we attempt to judge weights. When we lift a weight we experience a pull on our muscles. The mechanism is described as the muscle sense.

**SCRATCH REFLEX.** If a stimulus is applied to the saddle shaped area in a dog (shown in Fig. 240) the thigh is flexed and rhythmical movements of scratching are produced. The rhythm is approximately the same for the same animal, but varies somewhat with the size of the animal. The variation in rate is probably a mechanical effect in that the scratching will tend to occur at the rate at which the moving parts act as a pendulum. Less muscular force will be required if the movement is at the period determined by the weight and length of the moving parts. The reciprocal innervation and the tendency for afferent impulses from a muscle to inhibit that muscle help to maintain the rhythmical movements. The direction of scratching is in the direction of the area of skin stimulated.

**EXTENSOR THRUST.** If the ball of the toe of a flexed hind limb of a dog is gently pressed the leg is extended. This suggests one of the mechanisms of walking in that pressure of the ground against the foot will cause extension of the leg.

**FLEXION REFLEX.** If, on the other hand, the foot is pinched, the leg is drawn up as if to remove it from injury.

A large number of reflexes have been described, but they all show the same characters, each being an ordered whole due to the centres in the spinal cord correlating all the afferent impulses and sending out the appropriate efferent impulses.

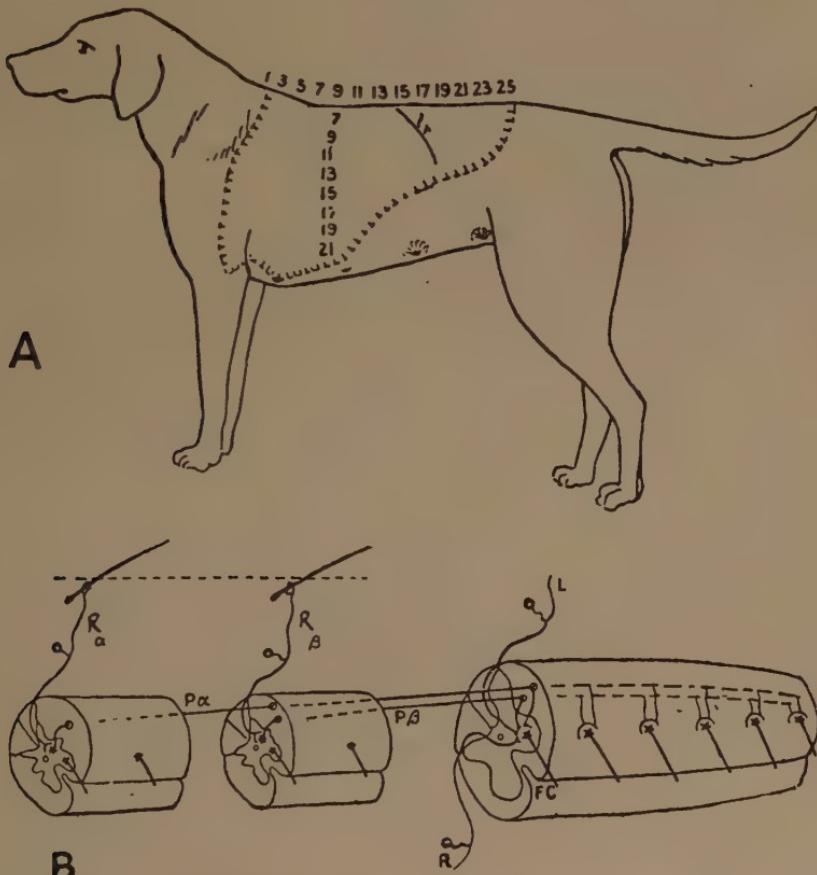


FIG. 240.—A, The Receptive Field for the Scratch Reflex as revealed after Low Cervical Transsection:  $lr$  marks Position of Last Rib. B, Diagram of Spinal Arcs involved in the Scratch Reflex.

$L$  = receptive or afferent path from left foot,  $R$  = receptive nerve-path from opposite foot,  $R\alpha$  and  $R\beta$  = receptive nerve-paths from dorsal skin of left side,  $FC$  = final common path in this case to a flexor muscle of the hip,  $P\alpha$  and  $P\beta$  = propriospinal neurons (from Sherrington's *Integrative Action of the Nervous System*, by permission of Yale University Press and Messrs. Constable & Co., Ltd.).

**Summation and Inhibition of Reflexes.** If stimuli are applied so that two reflexes should be produced we find that only one does in fact occur. This is due to the fact that the *final common path* down which all discharges must pass is the same, so that only one effect

can be produced at one time. If the two stimuli tend to produce similar movements they reinforce each other. This is the process known as *facilitation*. For example, if two spots on the scratch reflex area are stimulated it is possible to produce a reflex with stimuli so weak that neither by themselves would produce an effect. Further, the direction of scratching is between the two points stimulated, and if one stimulus is more effective or stronger than the other the movement will be more in the direction of that stimulus than the other. If on the other hand the two stimuli are antagonistic rivalry will occur and one or the other will produce an effect. That means that the reflex which does not occur is inhibited in order to allow the one that does occur to occupy the final common path.

It is possible nevertheless to produce algebraical summation of reflex effects. If stimuli are applied to the two sciatic nerves, and the movements of isolated extensors and flexors are recorded, it can be shown that both may be effective and that the degree of effect depends upon the strength of the two stimuli.

The prepotent stimulus depends on several conditions. It partly depends on the strength of the physical stimulus and partly upon the nature of the sensation which might be produced by the stimulation. Thus a stimulus which would produce a painful sensation tends to dominate a non-painful stimulus.

A response may result from two stimuli applied to two different afferent nerves, either of which would not produce a response. This is known as *induction*. On the other hand, if each of the stimuli were capable of producing an effect the resulting greater response is said to be due to facilitation.

### Equilibrium

The physics of the processes of equilibrium have been described on pages 10 to 16. For the maintenance of equilibrium the muscle sense is only one of the essential factors. The afferent impulses for this sense pass up the cord in the posterior columns, the dorsal spino-cerebellar and ventral spino-cerebellar tracts (see p. 357) to the cerebellum. Cutaneous sensations (pressure, etc.) also help to regulate the muscles. There are in addition important afferent impulses from special organs associated with the ear. In describing the auditory function of the ear we pointed out that the semi-circular canals, utricle and saccule, are concerned with the maintenance of equilibrium (p. 430). Two kinds of information are conveyed by the vestibular branch of the eighth nerve, namely, the position of the head at rest and the movements of the head.

MACULÆ OF UTRICLE AND SACCULE. The information as to the position of the head at rest is supplied by maculæ in the utricle

and saccule. These are slightly raised areas of cells with hair-like projections on the inner walls of the utricle and saccule. Nerve fibres ramify amongst these ciliated cells and amongst the cilia are concretions which by their weight stimulate the cells. Experimental proof for this view of their function is furnished by an experiment upon the crayfish (*Palæmon*). If the calcareous particles lying in the otolith organs are replaced by small particles of iron the effect of gravity will be the same as before.

If now a powerful magnet is held close to the animal the iron filings will be attracted so that the direction of pressure on the hair-like projections of the

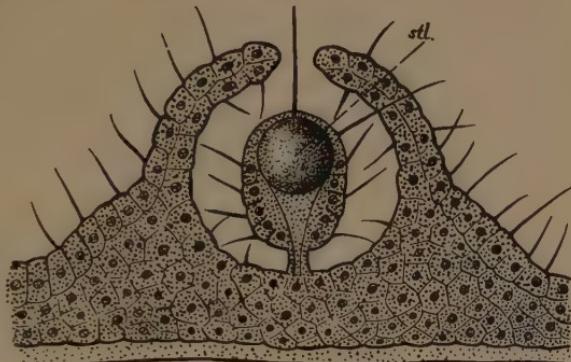


FIG. 241.—Tentaculocyst (Statocyst) of a Medusa (re-drawn after Hertwig from Dahlgren and Kepner).

*stl.* = statolith enclosed in a pedicle which sways with the animal's motion and affects the hairs which project from the surface.

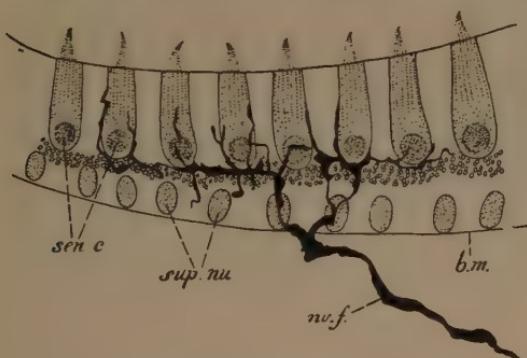


FIG. 242.—Portion of the Macula of a Mouse, treated by Golgi's Method to show Nerve-endings in the Sensory Cells (redrawn after V. Lenhossek from Dahlgren and Kepner).

*b.m.* = basement membrane, *sup.nu.* = nuclei of supporting cells, *nv.f.* = nerve fibre, *sen.c.* = sensory cells.

gravity and the animal stands in the corresponding attitude.

In some mammals the position of the otoliths is such that they must hang from the hair cells by their weight. The effect of gravity will be to cause these to act as pendulums. The stimulation will be

determined by the resultant of the action of gravity and the pull of the magnet. When the magnet is brought near, the animal stands as if the resultant were vertical and the level surface at an angle to the horizontal. In other words the afferent mechanism interprets the combined forces as being equivalent to

brought about by the movements of the hair cells, the vertical plane being indicated by the pull of gravity, and deflections from this plane will produce corresponding reflexes from the animal (Magnus and de Kleijn).

**Semicircular Canals** (Flourens, 1830). The semicircular canals are stimulated by movements of the head and they are placed in three planes at right-angles to each other. The two external canals are situated in a plane which is almost horizontal in the erect position of the human head. The two other pairs of canals are therefore vertical as they are at right-angles to the external canals. As they

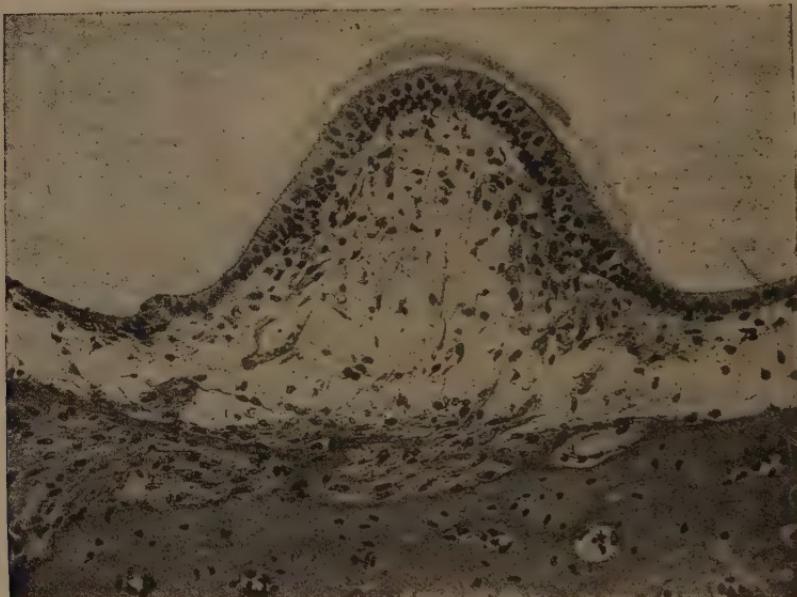


FIG. 243.—Photograph of a Section through Crista of the Ampulla of the Guinea-pig (H. Pringle, from Quain's *Anatomy*).

In the lowest part of the section nerve-fibres are seen passing through the bone to the loose tissue below the crista. The epithelial cells of the crista are pear-shaped surmounted by hairlets projecting into a mucinous material.

are also at right-angles to each other we must find out their positions in relation to the head. It is easy to remember the positions of the vertical canals as they are all at forty-five degrees to the sagittal plane. Thus the right anterior is parallel to the left posterior and the left anterior is parallel to the right posterior.

The membranous semicircular canals are held in the bony cavity by strands of connective tissue. They are lined by cubical epithelial cells and their area is about one-fifth of the bony canal in which they are contained.

At one end of each semicircular canal there is an ampulla pro-

jecting into which there is a raised fold called the crista acustica; the cristaæ acusticæ are covered by columnar epithelial cells with long filamentous projections. Nerve fibres ramify amongst these cells. As the anterior and posterior canals have a common opening the ampullæ must be at their external ends and the ampullæ of the external canals are at their anterior ends.

The arrangement of these canals in three planes has suggested a directional function. At one time they were supposed to indicate the direction of sound, but as all sound vibrations reach the internal ear in the same direction, i.e. down the external auditory meatus,

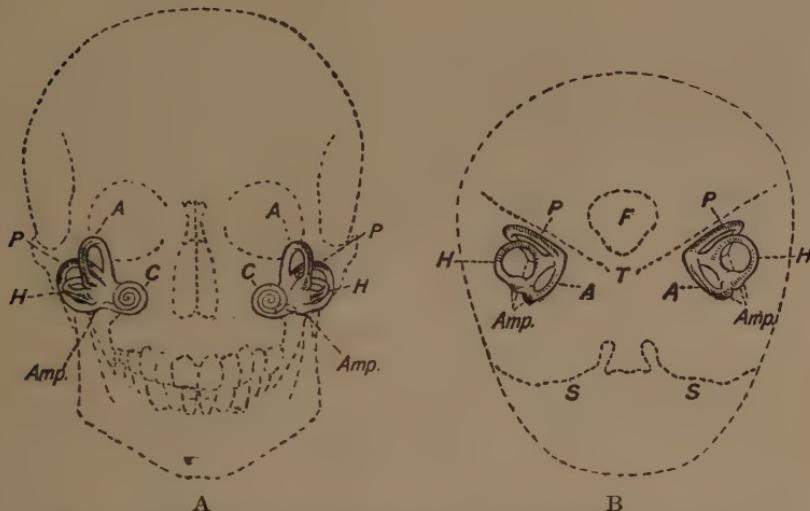


FIG. 244.—Sketches to show Position of Semicircular Canals in Head (drawn from specimens in the Museum of the Royal College of Surgeons by kind permission of Sir Arthur Keith).

The canals are enlarged relatively to the skull. A, View from front; B, from above, looking down on base of skull. A = anterior vertical canal, P = posterior vertical canal, H = horizontal canal, Amp. = ampullæ (the posterior one is not so well seen, as it is below and behind the others), C = cochlea, F = foramen magnum, T = ridge of temporal bone, S = sphenoid. Note that the two vertical canals are each at  $45^{\circ}$  to sagittal plane.

such function is impossible. They are now believed to indicate the direction of movement of the head, and movement in any direction must stimulate one or more of the canals according to the resolution of the movement into the directions of the various canals.

When movement occurs in the axis of a canal the endolymph lags behind, whilst the membranous canal moves until the liquid acquires momentum. When the movement decreases the momentum of the liquid causes it to move on, whilst the canal slows down. Therefore either positive or negative acceleration will cause movements of endolymph relative to the membranous canal. A jet of liquid issuing from the canal into the ampulla will impinge against the filamentous projections of the cells on the

crista acustica, thus causing afferent impulses in the nerve fibres in that region. As the canals are very narrow the friction between the walls and liquid is very great and there will be very little delay—between the starting and stopping of the movement of the liquid relative to the wall of the canal.

Experiments, by which this mode of stimulation was discovered,—were made on pigeons because their canals are easy of access. Destruction of a canal causes incessant movement in the plane of the destroyed canal as if there were nothing to check that movement.

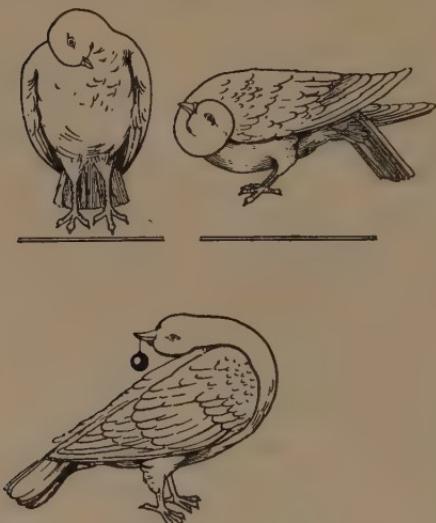


FIG. 245.—Effect of Destruction of the Labyrinth in a Pigeon (Flack and Hill).

Upper figures show effect of unilateral destruction on the muscular tone: that to left shows the result 5 days and that to the right 20 days after destruction of the labyrinth on the right side. Lower figure shows effect of bilateral destruction. A small shot, weighing 20 gm., is hung to the animal's beak by a thread. The shot swings with the animal's movements, and if it happens to get thrown over backwards the neck muscles are too weak and toneless to lift the head plus the small weight into a normal position.

through other senses such as sight and touch, because blindfolding the animal now causes return of the symptoms. Removal of the cerebrum in a pigeon causes no disorders of equilibrium, but after recovery from destruction of the semicircular canals removal of the cerebrum causes loss of equilibrium, which is then permanent.

Disturbances of equilibrium in man may occur as the result of injecting hot or cold water into the external auditory meatus, but one cannot draw any conclusion as to the function of the vestibular apparatus from such a mode of stimulation. In Menière's disease,

Injecting saline at body temperature in the direction of the ampulla causes movement of the head and eyes in the direction of the current (Ewald), whilst injection in the opposite direction, the canal in the direction of the ampulla being blocked, does not cause movement.

Destruction of the canals leads to loss of tone, so that in a pigeon with both sets of semicircular canals destroyed and with a small lead shot attached to its beak, if the lead shot swings so that the head is turned over backwards the pigeon cannot straighten its neck. Destruction on one side causes lack of tone on one side and consequent abnormal positions. After some months the animal recovers apparently by re-education

in which giddiness and disturbances of equilibrium (staggering) occur, there is destruction of the internal ear. The effect of rotation is difficult to understand as giddiness lasts for some time after the rotation stops: it may partly be of the nature of an after-image.

Owing to there being an ampulla only at one end of each canal movements with a component in the direction of the right anterior and left posterior canals will stimulate the right anterior when the movement commences towards the back and left and will stimulate

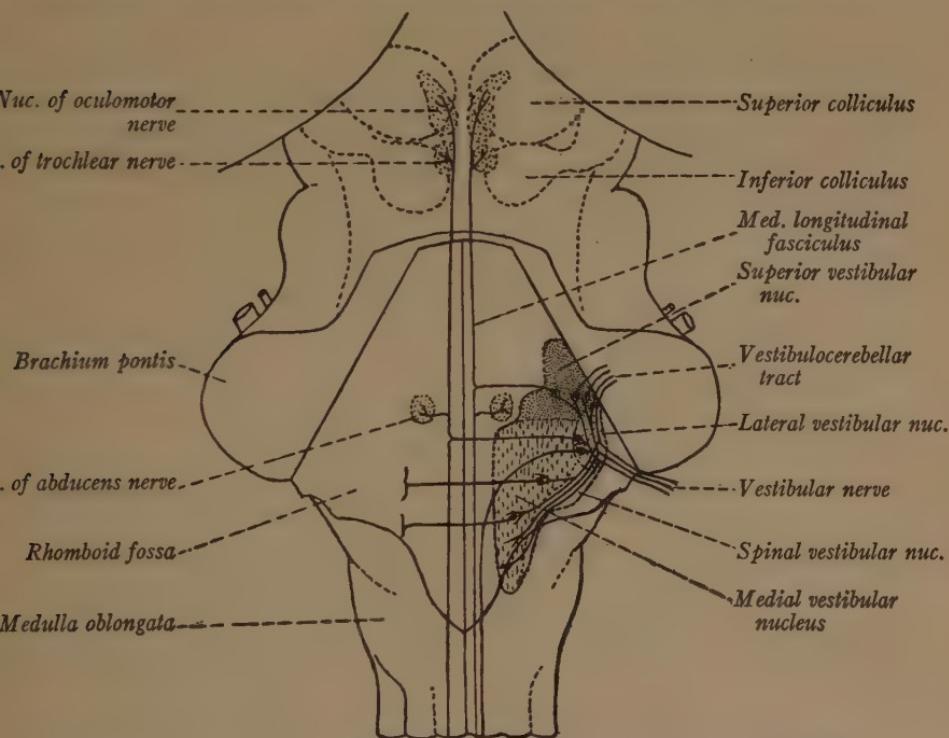


FIG. 246.—Diagram of the Nuclei and Central Connections of the Vestibular Nerve (Ranson, based on figures by Herrick and Weed).

the left posterior when the movement stops, but movement towards the front and right will stimulate the left posterior at the starting of the movement and the right superior when it stops.

**Central Connections of Vestibule.** Most of the impulses passing by the vestibular branch of the eighth nerve go to the cerebellum. There are a number of centres in the floor of the fourth ventricle by means of which the vestibular impulses are linked up with muscular activities.

We can distinguish two different conditions—the maintenance of

equilibrium, i.e. keeping the centre of gravity above the base of support, and the regulation of movements in which the centre of gravity may not always be above the base. Thus in turning on a bicycle the balance is maintained by the centre of gravity acting downwards inside the curve formed by the bicycle wheels and the horizontal component of the centrifugal force acting radially. The slope of the bicycle represents the direction of the resultant of the two forces.

**Cerebellum.** It is because the cerebellum is the head ganglion of the proprioceptive mechanism that its removal produces the paratonia, parasthenia and astasia described in Chapter XXVI. Interference with the afferent impulses to the cerebellum prevents the normal functioning of that organ. Thus destruction of the vestibules interferes with movement until re-education occurs through the cortex of the cerebrum : destruction of the posterior columns in locomotor ataxia leads to inco-ordination because of the absence of the muscle sense : as the cerebellum has no information as to the tension and length of the muscles it cannot regulate alterations in their tension and length. The cerebrum, however, may be able to help to regulate muscular movement under such circumstances through visual impulses.

The cerebellum sorts all the afferent impulses from cord, pons, cerebrum which pass up to the cortex by the afferent paths. The next stage is that the impulse is forwarded by Purkinje cells and their fibres to the dentate nucleus, whence they are relayed through the superior cerebellar peduncle to the contra-lateral red nucleus and cerebrum. It is these impulses that regulate the discharges to the muscles.

The posture maintained by the decerebrate animal is influenced by afferent impulses as shown in Fig. 247.

In addition to reflexes from the limbs two very important afferent paths are those from the labyrinth and from the neck as shown in the following examples. Rotation of the head to the right causes increased extension of the left side, i.e. the side to which the nose points with decrease in the tone of the muscles on the right side. Lateral flexion of the head causes increased tonus in the limbs of the side to which the head is bent. Dorsal flexion of the head in some animals causes extension of the fore-limbs and flexion of the hind-limbs : the animal sits up as if looking up at a high shelf. Ventral flexion of the head causes the fore-limbs to flex and the hind-limbs to extend as if the animal were looking under some low-lying object. As these postures are still obtained after bi-lateral destruction of the labyrinths they are ascribed to the proprioceptive endings in the neck muscles.

According to Magnus and de Kleijn unilateral destruction of the

labyrinths causes deviation of the eyes to the side of the lesion, and the head is turned to the same side. The rotation of the head causes the alterations in posture described above due to the proprioceptive endings in the neck muscles. The intact labyrinth appears to have a tonic effect on the contralateral neck muscles. The neck muscles on the uninjured side are atonic owing to the absence of the vestibule on the side which ought to control them, hence the rotation of the head to the side on which the labyrinth has been destroyed.

Magnus and de Kleijn have used preparations in which the cerebral cortex, including the corpora striata, are removed leaving

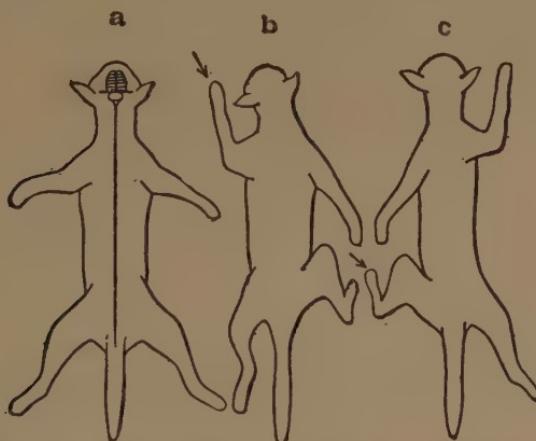


FIG. 247.—Showing that an Animal Responds to a Stimulation by an Attitude of the Whole Body (Sherrington, *Integrative Action of the Nervous System*, Yale University Press).

*a*, position under decerebrate rigidity; *b*, change of attitude from *a* evoked by stimulation of left forefoot; *c*, change of attitude from *a* evoked by stimulation of left hind-foot.

the optic thalami and subthalamic region intact. These animals do not show decerebrate rigidity. They show normal motor reactions if disturbed, but if left to themselves remain motionless.

The reflex mechanisms which regulate the position of such an animal are those just described, namely, labyrinthine and neck reflexes to which are added the stimuli from the body wall and limbs. Unsymmetrical stimuli such as those produced by the animal lying on its side cause the animal to right itself.

In the decerebrate animal the animal does not maintain normal postures, but can stand only when placed with its limbs wide apart.

The centres for postural reflexes are therefore in the part of the brain between the thalami and the inferior corpora quadrigemina. They persist after removal of the cerebellum, therefore the

paths for their maintenance do not pass through the cerebellum.

In the monkey the eyes have a special importance as they can compensate for the loss of both labyrinths.

The cerebellum appears not to be essential for the postural reflexes, but with the forebrain intact injury to the cerebellum interferes with the performance of movements, and it may be that the cerebellum regulates movements initiated from the cortex.

Loss of stimuli from eyes, labyrinth, skin or muscles may lead to loss of equilibrium in man. Frequently compensatory re-education minimizes such deficiencies, especially if the loss has occurred slowly. In locomotor ataxia the dorsal columns of the spinal cord become degenerated. Individuals suffering from this disease lack the proprioceptive impulses which should ascend the tracts in this region. Their equilibrium is maintained largely by visual impulses, and if their eyes are closed they lose their balance. As the control through the eyes is not so efficient as in the normal condition persons afflicted with this disease easily become fatigued.

Loss of one channel by which impulses arrive hampers but does not upset the reflex postural reactions. The effect of loss of one kind of impulse varies with the importance of that channel, whilst loss of two kinds of impulses shows more marked effects.

Unusual or excessive stimuli affect the equilibrium of the intact human individual. For instance, some people become dizzy when looking down from a high elevation. This may be the result of undue influence being exercised by visual sensations : absence of near objects on which the eyes may be fixed may be a factor in such feelings of dizziness. Seasickness is ascribed to abnormal stimulation of the labyrinth or to lack of correlation of visual and labyrinthine impulses.

Drugs, e.g. alcohol, may affect the proper functioning of the mechanism of equilibrium. Lack of co-ordination is probably due to blocking of impulses at the synapses or to the improper functioning of the cortical cells in the outer cell layer of the various "psychic" areas.

There is a close relationship between the movements of the eyes, head and neck ; thus there is a special tract, the medial longitudinal bundle, which links up the superior corpora quadrigemina, the vestibular impulses (Deiter's nucleus), and the afferent impulses from the neck muscles with the motor nuclei for the eye muscles.

The extrinsic eye muscles present a high degree of co-ordination as they are required for the rapid and accurate performance of eye movements. In addition to afferent impulses from the extrinsic eye muscles visual impulses from the retina pass to the superior

corpora quadrigemina, thence to the motor nuclei of the eye muscles.

In this chapter we have studied the way in which muscular movements are integrated. The muscles can be regulated first of all because afferent stimuli from themselves convey information as to their tension and length. Upon this basis the spinal cord regulates muscle contraction to produce definite reflex movements. This requires the contraction of some muscles and relaxation of others. When two antagonistic reflexes might occur we find that one is suppressed by inhibition.

For the regulation of this complex mechanism the cord has been supplemented by the brain stem and cerebellum which has a general inhibitive and directive influence on the whole cord just as the cord inhibits and directs the different groups of muscles.

We do not yet know how impulses are sorted by the synapses so that one inhibits or reinforces another, thus regulating this complex mechanism, but it is quite certain that from a multitude of afferent impulses the nervous system builds up a complete whole with the appropriate discharge of efferent impulses. To this subject we shall return in Chapter XXXIX.

NOTE.—Those students who desire further information on the subject of this chapter should consult S. S. Maxwell, *Labyrinth and Equilibrium* (J. B. Lippincott), in which the view is advanced that it is tension on the maculae and ampullæ which acts as the stimulus to these structures.

## CHAPTER XXXIII

### INTEGRATION OF RESPIRATION

The object of respiration is to obtain oxygen and to get rid of carbon dioxide. In order that this may be accomplished the blood must convey oxygen and remove carbon dioxide; this problem has been discussed in Chapter XIX. In the present chapter we are concerned only with the regulation of respiration.

When one breathes air containing a minute increase in carbon dioxide or a great deficiency in oxygen the volume of air breathed is increased and it can be shown that the amount of carbon dioxide is a more delicate regulator of respiration than is the change in oxygen concentration.

If an animal breathes air containing an increased amount of

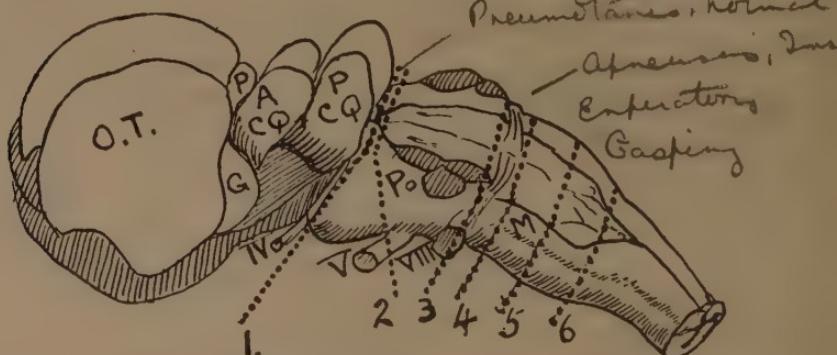


FIG. 248.—Diagram of Brain Stem showing Levels at which Sections were made (Lumsden, *Journal of Physiology*).

Section above 1 produces no appreciable effect. Section between 2 and 3 causes the inspiratory type of breathing (apneusis). Section between 3 and 4 causes a gasping type of respiration. Section between 5 and 6 causes cessation of all respiratory movements.

carbon dioxide the respirations increase both in depth and in frequency; on the other hand if the vagi are cut the result is a decrease in frequency. This points to two influences on respiratory movements, namely, a chemical influence due to carbon dioxide and a nervous influence through the vagi.

**Respiratory Centre.** If the brain stem is cut across below the level of the *calmus scriptorius* the respirations cease (cross section 5, Fig. 248), but if sections are made at higher levels, various modifi-

cations of the respiratory movements occur. Lumsden has recently investigated this subject and he finds that there are the following centres :—

1. A gasping centre situated between the lines 5 and 6 in Fig. 248. This centre is stimulated by lack of oxygen and by excess of carbon dioxide.
2. An expiratory centre situated between the lines 4 and 5, which is stimulated by excess of carbon dioxide ; lack of oxygen impairs its vitality.
3. A centre which produces prolonged inspiratory spasm, apneusis.

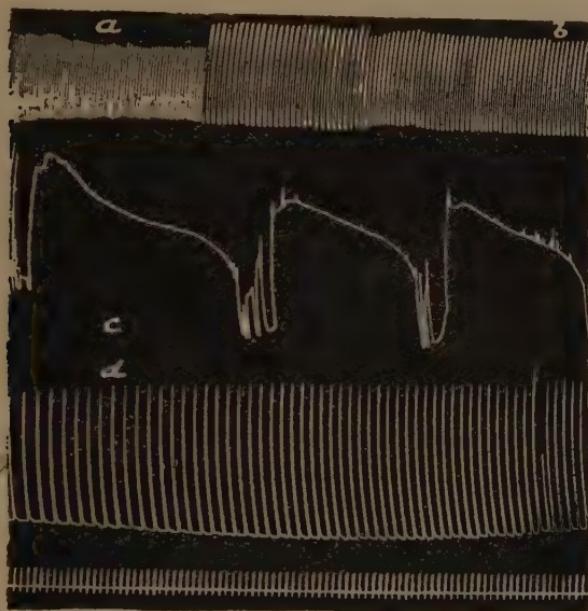


FIG. 249.—Tracings of Various Types of Respiration in the Cat (Lumsden in *Journal of Physiology*).

(a) normal ; (b) after vagotomy ; (c) prolonged inspiratory tonus (apneusis) and gasps after section at 2, Fig. 248 ; (d) gasping. Time tracing at 5-sec. intervals. Inspiration upwards. Tracings read from left to right.

This apneustic centre is situated between the lines 3 and 4. It is stimulated by excess of carbon dioxide and less effectively by moderate lack of oxygen.

4. A centre which controls apneusis and allows the normal respiration to occur (Pneumotaxic centre), situated between the lines 1 and 2.

His experiments show that the respiratory movements are controlled by nerve cells situated between the various sections. The centres described above are not unlike those concerned in

reflex action. In the cord are local centres for reflexes which produce both contraction and relaxation of muscles, corresponding to the gasping and expiratory centres described by Lumsden ; in the brain stem are centres which produce decerebrate rigidity corresponding to the condition of apneusis ; and finally in the basal ganglia are centres which abolish decerebrate rigidity and produce normal postural reflexes. This effect corresponds to the centre which regulates apneusis.

*Normal A E G*

The series of control stations is apparently necessary for the performance of normal actions, each higher centre controlling those at a lower level.

### Nervous Regulation of Respiration

In the regulation of reflexes we found that impulses from the muscles themselves, from the internal ear and from other parts of the nervous system are all concerned. Likewise in respiration impulses from all parts may affect respiration. Cold water or cold air applied to the skin causes gasping, excitement causes quickened respiration and swallowing causes inhibition of respiration. Further it is possible to inhibit respiration for a short time by a voluntary effort ; this is called false apnea (apnoea spuria), because it is an interference by voluntary control with a non-voluntary process.

Such factors as are mentioned in the preceding paragraph are comparable to the control of reflexes by voluntary or other influence, but there is one nervous influence which requires special description. We mentioned above that cutting the vagi interferes with the rate of respiration even when excess of carbon dioxide is breathed, and we shall now show that this effect is caused through cutting off influences from the lungs themselves.

Löwy (1888) caused collapse of one lung and then he cut the vagus on the opposite side. This operation caused the frequency of respiration to be reduced just as if both vagi had been cut and subsequent cutting of the vagus on the side of the collapsed lung produced no further effect. If the collapsed lung were distended with air or hydrogen, its vagus remaining uncut, the respirations returned to their original frequency. By isolating a strip of the diaphragm in a rabbit Head was able to demonstrate the contractions of the diaphragm independently of the state of expansion or contraction of the chest itself. Thus repeatedly distending the lungs with air which mechanically causes the inspiratory position of the chest is accompanied by relaxation of the isolated strip of diaphragm which indicates an expiratory discharge from the nervous system. On the other hand repeatedly drawing air out of the chest causes a mechanical condition of expiration, but the isolated strip contracts,

showing an inspiratory discharge from the nervous system. Cutting both vagi abolishes this effect on the isolated portion of the diaphragm. This mechanism should be compared with that by which a muscle is regulated by nerve endings in itself ; the difference is that in the respiratory mechanism it is impulses up the vagi which regulate a movement brought about by a series of muscles. The adequate stimulus is believed to be the state of stretching or shrinkage of the alveoli of the lung, the degree of expansion in these taking the place of the length and tension of muscle in the reflex posture or reflex movement of muscle.

This stoppage of respiration by impulses passing up the vagi is known as *Apnoea vagi*. That this factor plays a part during normal breathing is shown by recording the electrical changes in the vagus. It is found that an electrical change is recorded at the end of each

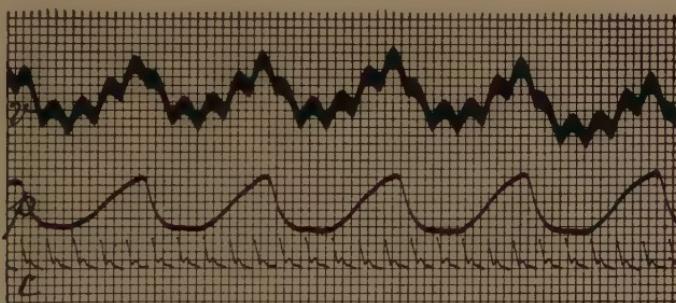


FIG. 250.—Figure showing the Electrical Changes in the Vagus Nerve which accompany the Respiratory and Heart Movements (*Einthoven*).

*v* = electrovagogram, *p* = respiration record (up, inspiration; down, expiration), *c* = pulse record.

inspiration and also at the end of expiration when the expirations are deep. From these electrical changes one deduces that there is an impulse up the vagus at the end of each inspiration and at the end of each deep expiration. The student must recollect that normal inspirations are muscular, whilst expirations are mainly passive unless forced, when muscular factors are brought into action (see p. 54). Thus he will realize that normal distension of the alveoli of the lung apparently produces inhibition of the muscular movements which cause inspiration, but as there is no muscular movement in quiet expiration it is only with deep expirations that an impulse up the vagus is required to inhibit expiration.

### Chemical Regulation of Respiration

Just as the nervous regulation is a special case of the regulation of reflexes so the chemical regulation of respiration is a special case

of the influence of drugs on nerve tissue (cf. p. 325). We have already seen that carbon dioxide in the inspired air increases pulmonary ventilation. The result is that the composition of the alveolar air is kept near to a standard composition which is fixed for each individual. Haldane and Priestly found that a variation of 2 mm. in carbon dioxide tension increases the pulmonary ventilation by 100 per cent.

The blood leaving the lungs is in equilibrium with the alveolar air and the problem as to whether carbon dioxide produces its effect by acting on the lung epithelium or by a change in the composition of the blood was decided by Fredericq. His experiment was the crossing of the circulation of two dogs so that the blood coming from the lungs of one passed by the carotid of the other to its brain and vice versa. By making dog A breathe air containing excess of carbon dioxide the brain of dog B received blood containing excess of carbon dioxide. The respiration of dog B was increased, whilst that of dog A was decreased, because the excessive respiration of B resulted in a decrease in carbon dioxide in the blood coming from the lungs of B which went by the crossed circulation to the brain of A.

The effect of decreasing the amount of carbon dioxide in the blood can be shown in man by forced respirations. If one breathes deeply and quickly the extra ventilation causes a decrease in carbon dioxide pressure in the alveolar air, hence a more rapid escape of carbon dioxide from the blood during its passage through the pulmonary circulation. After such a period of forced respiration breathing stops and there is no attempt to breathe for an appreciable interval of time. This pause in respiration is known as true apnoea (apnoea vera), because it is not forced on the respiratory centre by voluntary inhibition of the activity of the respiratory centre.

At first one might be inclined to ascribe the effect of carbon dioxide to some special property in itself, but the effect may be due to the acidity of the blood. When carbon dioxide is dissolved in water it forms carbonic acid; this, by dissociation, yields hydrogen ions and bicarbonate ions, according to the mass law equation,  $C_H \times C_{HCO_3} = KC_{H_2CO_3}$  (see p. 225).

In the blood there is a certain amount of sodium bicarbonate which is fairly well ionized, whence one frequently rearranges the above equation to represent the acidity of the blood as

$$C_H = K \frac{C_{H_2CO_3}}{C_{BHCO_3}} \text{ where } B \text{ stands for any base}$$

or  $C_H = K_1 \frac{\text{Pressure of carbon dioxide in alveolar air}}{\text{concentration of bicarbonate in blood}}$ , where  $K_1$  includes a factor relating the concentration of carbonic acid to the alveolar carbon dioxide pressure and one for the degree of dissociation of sodium bicarbonate.

By adding a non-volatile acid to blood carbon dioxide is set free and easily escapes through the lungs, but the amount of  $\text{BHCO}_3$  is decreased ; if the acidity of the blood is kept constant by the respiratory centre the concentration of carbonic acid must decrease to balance the concentration of bicarbonates in the above equation ; there should therefore be a fall in alveolar carbon dioxide tension, and this is found to be the case.

Thus the experimental results can be explained on the ground that the respiratory centre responds to the hydrogen ion concentration of the blood which in turn can be affected by the pressure of carbon dioxide in the alveolar air.

### Fundamental Rhythmic Activity of Respiratory Centre

Although the activity of the respiratory centre is regulated by nervous and chemical influences its rhythmic discharge is probably merely altered by such influences. In order to show that the action of the respiratory centre is independent of other nervous influences it has been almost isolated by the following operative procedures.

The cord was cut below the exit of the phrenic nerves and the posterior roots of the remaining cervical nerves were cut. Thus all afferent impulses from the cord were excluded. The brain stem was cut at the level of the superior corpora quadrigemina by which impulses from the cerebrum were excluded. Finally the vagi were cut, thus excluding the impulses from the viscera through these nerves.

After such operative procedures the rhythmic movements of the diaphragm continue, showing that the centre is still acting rhythmically. Although afferent stimuli may continue to reach the centre, e.g. by the eighth nerve, one cannot see how these stimuli can produce rhythmic responses in a centre. One therefore concludes that the rhythmic action of the respiratory centre is inherent in the centre just as the rhythmic activity of the heart is a property of that organ.

**Special Respiratory Movements.** The respiratory movements are modified in many ways. We have already pointed out that they are inhibited during swallowing. This inhibition usually occurs at the end of inspiration, but in any case it is followed by an expiratory movement which thus tends to prevent entrance of foreign bodies into the respiratory passages. Cold applications usually produce a spasmotic respiratory movement or a gasp. Irritation of the nose causes a violent expiration through the nose or a sneeze. Irritation of the larynx is followed by a violent expiration at the end of which there is a sudden opening of the glottis or a cough. Sighing and sobbing are also modified respira-

tory movements. The modified respirations of speech have been already described (Chapter XXXI).

*Cheyne Stokes Respiration.* A special form of respiration consists of a series of respiratory movements increasing to a maximum then decreasing to vanishing point. After a pause the series recommences. All stages may be found from a normal respiratory rhythm to that shown in Fig. 251.

The cause of this condition seems to be lack of sensitivity of the respiratory centre.

Cheyne-Stokes respiration sometimes follows the apnoea due to forced breathing. It can always be produced by the following experimental procedure (Haldane) : Breathe through an absorber containing alkali on the far side of which is a long tube to increase the dead space.

On breathing through this apparatus the air is breathed in and



FIG. 251.—Record of Cheyne-Stokes Respiration.

The end of a previous period of respiration is seen, then a pause. After the pause the respirations commence, increase to a maximum and decrease until another pause occurs. Usually the rate of respiration increases and decreases with the amplitude. (*Kindly lent by Dr. John Parkinson.*)

out of an enlarged dead space. The carbon dioxide is removed by alkali, and there is a progressive decrease in oxygen in the respired air, which ultimately causes increased respiratory movements. Increased movements cause a larger quantity of air to be breathed at each respiration, thus the effect of the larger dead space is overcome and more oxygen enters the lungs. The carbon dioxide has been washed out during the increased breathing, so a state of apnoea follows.

The centre behaves like an engine without a governor in that the respirations show periodic increases and decreases.

**Influence of Oxygen on Respiratory Movements.** A moderate decrease in oxygen tension does not markedly affect the respiratory movements, but a more marked decrease does increase the pulmonary ventilation. One view of this action is that the lack of oxygen increases the sensitivity of the respiratory centre to carbon dioxide. Another explanation is that deficiency of oxygen causes defective oxidation with the production of lactic and perhaps other acids. These acids increase the hydrogen ion concentration of the respiratory centre, thus causing an increase in respiratory movements.

The experiment described above is explained by assuming that

lack of oxygen causes the production of acids. When the respiratory movements increase so that fresh oxygen enters the lungs the acids are removed. This leaves a deficiency of hydrogen ions as the carbon dioxide has been washed out, hence apnæa occurs until carbon dioxide accumulates in sufficient quantity to cause the respirations to recommence.

At present the generally accepted view is that which was described above as due to the production of acids by anaerobic processes such as are known to occur in muscle.

Other explanations are less definite than the above. Haldane states that lack of oxygen increases the sensitivity of the centre to carbon dioxide. Henderson and Haggard claim that lack of oxygen causes the production of some substance which they call "respiratory X."

The action of haemoglobin and oxyhaemoglobin as acids may explain the effect of lack of oxygen on respiration. If the oxygen pressure in the alveolar air is low there will be less oxyhaemoglobin formed, and therefore less carbon dioxide will be displaced from the blood passing through the lungs as less alkali will be taken away by the stronger acid, oxyhaemoglobin (see p. 257). When this less oxygenated blood reaches the tissues there will be less oxygen available for the tissues and at the same time there will be less alkali available to combine with carbon dioxide.

Therefore for the same amount of carbon dioxide produced in the tissue there will be more free carbon dioxide left to raise the hydrogen ion concentration of the blood and tissues.

The hydrogen ion concentration of the blood may not be the only factor to be considered as it has been stated that at high altitudes no abnormal acids are present in blood. One must not lose sight of the fact that it is the hydrogen ion concentration in the centres that regulates their activity. In the case of exchanges between oxyhaemoglobin and carbon dioxide mentioned in the preceding paragraph there is not necessarily any change in the reaction of arterial blood.

A sudden, marked lack of oxygen such as occurs on breathing pure nitrogen causes stoppage of the respiration and tonic contraction of the striated muscles. This, however, is an abnormal state and may not be related to the normal control of respiration.

Respiration is thus seen to be regulated :—

(a) By nervous influences of which the most important are impulses passing up the vagi.

(b) By the pressure of carbon dioxide in the alveolar air.

(c) By marked decrease in pressure of oxygen in the alveolar air.

That excess of carbon dioxide acts by increasing the hydrogen ion concentration of the blood is indicated by experiments in which the hydrogen ion and carbon dioxide pressures have been varied independently. This may be accomplished by altering the concentration of bicarbonates in a fluid. Experiments carried out by altering the constituents of seawater showed that the respiration of a fish is affected more by the hydrogen ion concentration than by the pressure of carbon dioxide (Roaf). Similar experiments by perfusion of the medulla of new-born rabbits indicate that the hydrogen ion concentration is more important than the pressure of carbon dioxide in affecting the respiratory movements (Winterstein).

## CHAPTER XXXIV

### INTEGRATION OF THE CIRCULATION

The necessity for a variable circulation is the alteration in the oxygen requirements of the tissues ; the removal of waste products and the supply of fresh food material are less urgent and do not require such marked variations in blood flow, but they are equally important in the long run.

For the maintenance of the blood pressure three factors are required. Firstly, the heart must contract with sufficient force and frequency ; secondly, the heart must receive a sufficient volume of blood so that its beat can produce a reasonable output into the arteries ; and thirdly, the blood must be prevented from escaping too rapidly from the arteries. There are so many factors involved in these processes that one can indicate only some of them.

The principles of regulation are the same as those for the integration of reflexes and of respiration. There are special centres in the medulla known as the vaso-motor and cardio-inhibitory centres for the regulation of the escape of blood from the blood-vessels and for the regulation of the heart beat respectively. It is not known if there is any special chemical regulation of these centres, but drugs and the reaction of the blood affect them as they do any other cells.

**Effect of Gravity on the Circulation.** In the upright position hydrostatic pressure would cause the blood to collect in the lower limbs. This tendency is counteracted in two ways. If the blood-vessels to the lower limbs are slightly constricted less blood will pass through them, therefore enough blood is retained to maintain sufficient pressure to force blood up to the brain. This merely means that the relation of pressure to volume flowing through the vessels is kept such that too much blood does not pass away by the vessels of the lower limbs. On the other hand no amount of constriction of arteries can prevent the effects of gravity on the venous return of blood. The venous return is helped by the presence of the valves in the veins. Every muscular movement squeezes the veins by compressing them between the muscles and the surrounding structures, e.g. other muscles or the skin. The blood in the compressed veins is squeezed towards the heart because the valves

prevent movement in the opposite direction. When the muscles relax the blood cannot fall back, so the emptied veins are filled by

blood in neighbouring veins which is at a higher pressure. By this process the capillary blood pressure in the foot is not much in excess of that in the hand.

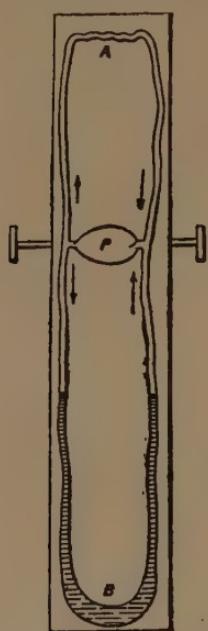


FIG. 252.—Artificial Schema to show Effect of Gravity on the Circulation (L. Hill).

The effect of gravity on the circulation can be illustrated in an eel (cf. Fig. 253). If it is suspended in air the heart is not supplied with blood and the circulation stops. If, however, a tall vessel full of water is passed up round the eel the hydrostatic pressure of the water presses the blood up to the heart and the circulation is restored. Again, a tame rabbit will die if held up by its ears, because blood gravitates into its flabby abdomen, whilst a wild rabbit with its firmer abdomen maintains a sufficient supply of blood to the heart.

Anæsthesia interferes with the normal regulation of the circulation in respect to gravity.

*Fainting* is due to deficient supply of blood to the brain, the result of too low a blood pressure, which in turn may be due to an insufficient return of blood by the veins.

The supply of blood to the brain may be increased by placing the person in a horizontal position, whereby the effect of gravity is eliminated. Another method of treatment is to make the person



FIG. 253.—Effect of Gravity on Aortic Blood Pressure in a Dog with Spinal Cord divided at the Level of the First Dorsal Vertebra (L. Hill from Schafer's *Text-Book of Physiology*. Oxford Medical Publications).

A = vertical feet-down position, B-C = effect of abdominal compression, D = horizontal position. Read from left to right.

sit down and bend forward with his head between his knees. This position puts the head below the level of the heart, and at the same time the abdomen is compressed. A flabby abdominal wall is one of the causes for stagnation of blood.

Muscular contractions of the walls of veins may also aid the return of blood to the heart. In the wings of bats there are rhythmically contracting veins to aid the circulation in the thin membranous structures. There is no evidence that rhythmical contractions occur in the veins of man.

**The Origin and Sequence of the Heart Beat.** The fact that the excised heart beats if supplied at the right temperature with an appropriate perfusion fluid shows that it can beat independently of the central nervous system, but there has been considerable discussion as to whether the heart beat is due to intrinsic nerve cells (neurogenic origin), or whether it is a property of the heart muscle itself (myogenic origin). The balance of evidence appears to be in favour of the latter view for the following reasons :—

1. The heart of an embryo chick beats rhythmically before nerve cells have grown into it.
2. A nerve-free portion of the tip of the ventricle of a frog or a tortoise will contract rhythmically.
3. Skeletal muscle will show rhythmical contractions if placed in Biedermann's fluid.

In invertebrates it may be that the heart beat depends upon nervous tissues, but in the mammal the evidence is that the rhythmical beat is a property of the cardiac muscle.

In a normally contracting heart the beat commences near the junction of the superior vena cava with the auricle. This has been

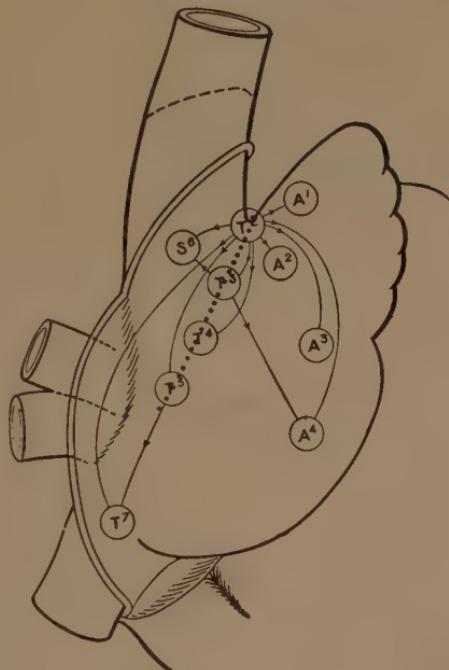


FIG. 254.—Electrical Method to measure Direction of Spread of Auricular Contraction (Lewis).

$T^1$  = the point which first becomes negative, therefore the starting-point of the auricular contraction  $T$  = leads from tenia,  $S$  = lead from sinus,  $A$  = leads from auricle.

demonstrated by recording the spread of the contraction and spread of the electrical changes over the surface of the auricle. The times at which the electrical changes reach various parts of the auricle

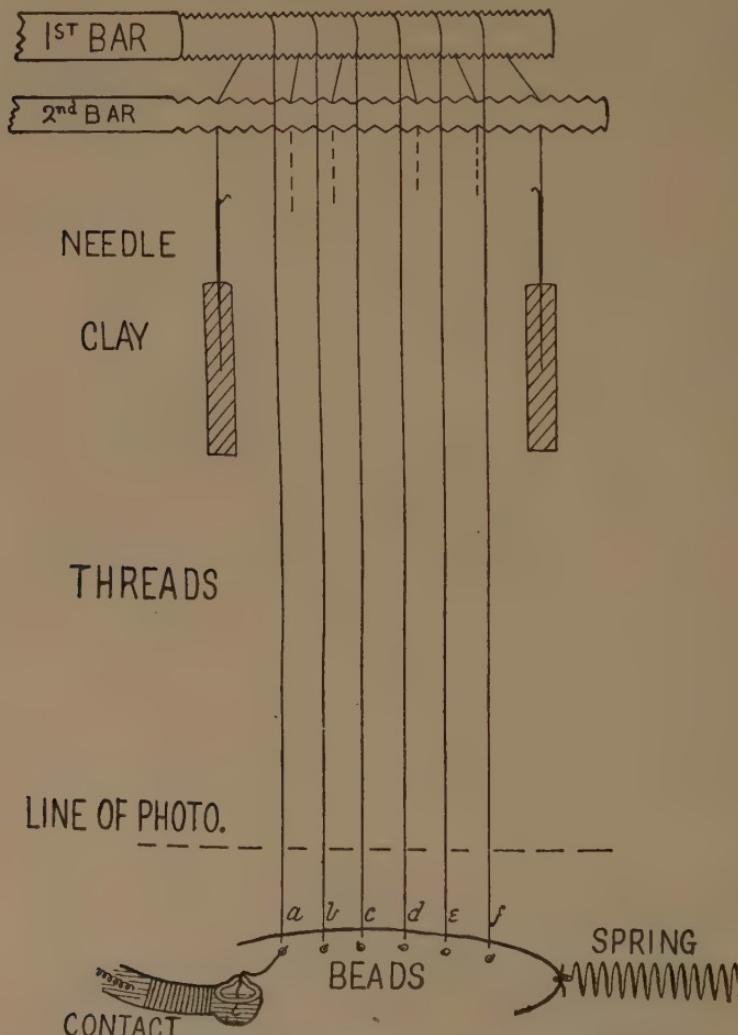


FIG. 255.—Apparatus to show Propagation of Wave of Contraction over the Auricle, Polymyograph (Lewis in *Heart*).

Six threads (*a-f*) are passed through the auricular appendix, the tip of which is balanced by a spring, and they are secured by tying on to beads. The threads are held vertical by stretching them over a bar by clay weights. If a portion of the auricle between two threads contracts, the threads are drawn closer together, and if a neighbouring part of the muscle is relaxed, it may be stretched and the threads attached thereto drawn apart. The shadows of the threads are photographed on a moving surface. One non-polarizable electrode is shown attached to *a*.

show the direction of spread and that the contraction always starts from one point. The area from which the contraction spreads is characterized by some primitive muscle-fibres supposed to be a

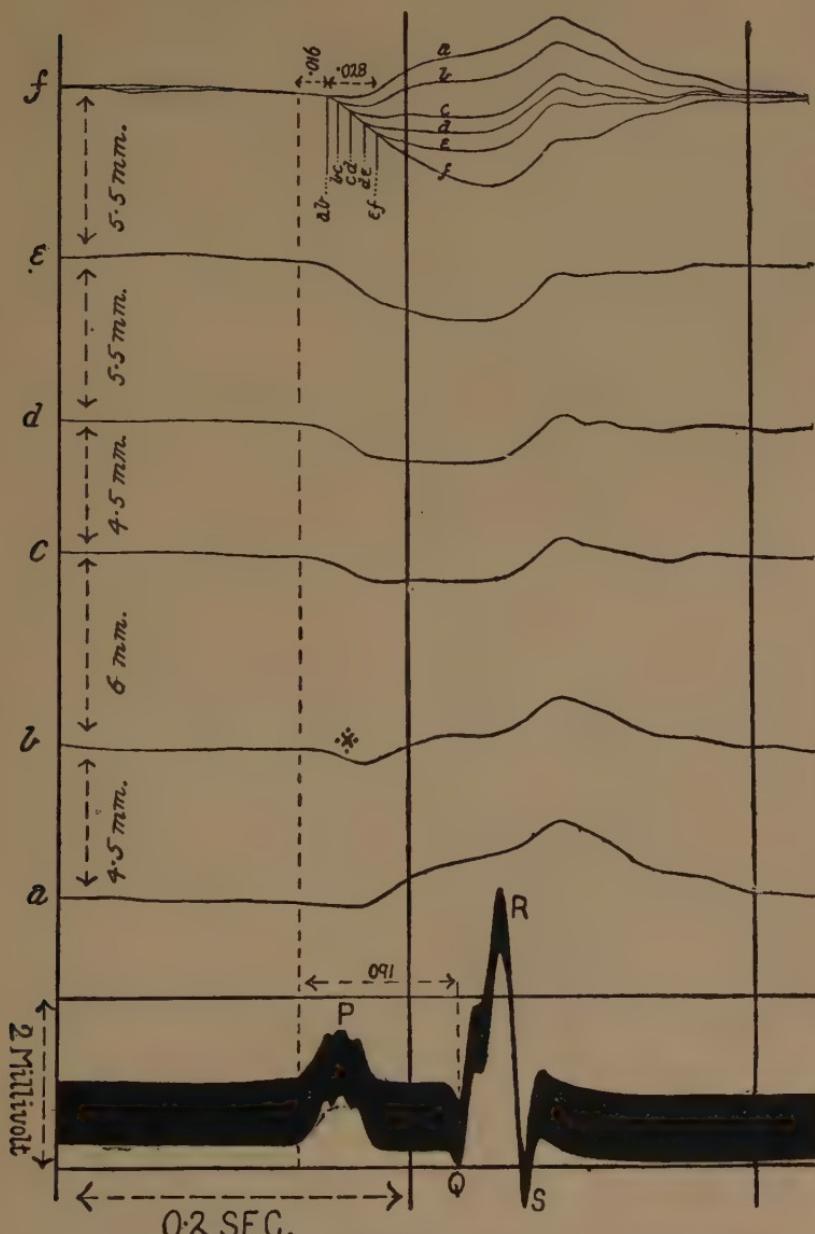


FIG. 256.—Enlarged Tracing of Photograph taken by Apparatus shown in Fig. 255 (Lewis in Heart).

The electrocardiogram below shows the time relations of the cardiac contractions; the P-R interval measures 0.091 of a second. The lines traced by the movements of the threads are superimposed on *f*. The segment *a-b* contracts first pulling all the threads towards *a*, as the segments *b-c*, *c-d*, *d-e* and *e-f* contract in succession *a* and *f* are drawn closer and closer together. By superimposing the curves it is possible to show the time at which the contraction reaches each segment, as now the drawing together of the threads will show as divergencies of the curves. The time at which the segments commence to contract is shown by lines drawn downwards from the superimposed curves.

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of  
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Experiments

remnant of the sinus and it is called the sino-auricular node.

In addition to measurements of the time intervals at which electrical changes reach different parts of the auricle Lewis has also shown the spread of contraction. A series of threads are attached to the auricle. The other ends of the threads are suspended by weights over a bar. The shadows of the threads are thrown on a photographic plate. The positions of the shadows indicate when the various parts of the heart muscle contract. Contraction between two threads draws them closer together and neighbouring parts if not contracting may be drawn apart, widening the interval between the neighbouring threads.

Measurements made by this method show that the normal contraction commences at the sino-auricular node. As the rate at which this initiates impulses determines the rate of the heart beat it is called the pacemaker.

From the sino-auricular node the contraction wave spreads by muscular conduction over the whole of the auricle, but owing to the fibrous division between the auricles and ventricles there are only two bridges of tissue by which the impulse can be carried on to the ventricle. These were discovered by Stanley Kent. One of these bridges, known as the auriculo-ventricular bundle, begins in a mass of tissue called the auriculo-ventricular node from which it runs along the inter-auricular septum to the inter-ventricular septum. The bundle divides into two and is distributed to the whole of both ventricles, one large division crossing the right ventricle in the moderator band. The bundle is formed of special fibres known as Purkinje fibres, which are large cells with striated margins and two nuclei. The function of the second bridge is unknown.

The contraction wave which spreads over the auricle stimulates the auriculo-ventricular node on reaching it, and an impulse passes along the auriculo-ventricular bundle at a rate greater than that of the conduction of a wave in muscle. Thus the whole of both ventricles are caused to contract at almost the same time.

The difference in contraction of the auricles and ventricles is due to the manner in which the contraction occurs in each. In the auricles the contraction spreads from the venous openings so that the veins are more or less closed, thus limiting the regurgitation of blood. The contraction wave moves like a peristaltic wave causing onward movement of blood so that the ventricles are filled not so much by pressure as by the kinetic energy of the blood set in motion by the contraction wave passing over the auricles.

The contraction of the ventricles on the other hand is almost simultaneous and forces blood out by the pressure produced in the cavities. The rapid spread of contraction in the ventricles is dependent on the distribution of the auriculo-ventricular bundle.

The time-interval between the commencement of contraction of the auricle and commencement of contraction of the ventricle is due to the spread of the contraction wave over the auricle to the auriculo-ventricular node and the conduction of the impulse from the auriculo-ventricular node through the auriculo-ventricular bundle to the ventricular muscle. Irregularities of the heart beat are due to interference with this normal sequence.

*Auricular Flutter.* Normally the contraction passes over the auricle uniformly, so that when it reaches the extremity of the auricle the wave is prevented from returning by the refractory phase of the muscle which has just contracted. If for some reason the wave starts in one direction only it can pass round the auricle down one side and up the other, and will thus ultimately return to its starting point.

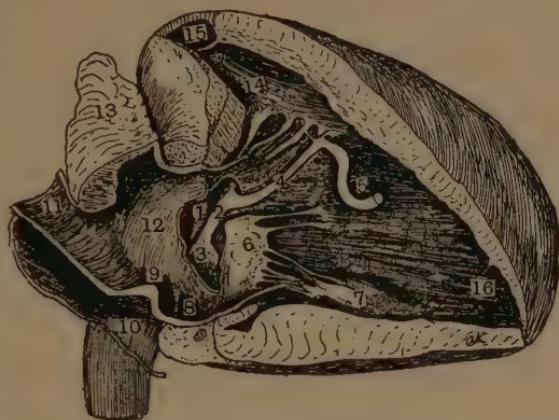


FIG. 257.—Right Auricle and Ventricle of Calf (Keith and Flack).

1 = central cartilage, 2 = main A-V. bundle, 3 = A-V. node, 4 = right septal division of A-V. bundle, 5 = moderator band, 6 = A-V. valve, 7 = papillary muscle, 8 = orifice of coronary sinus.

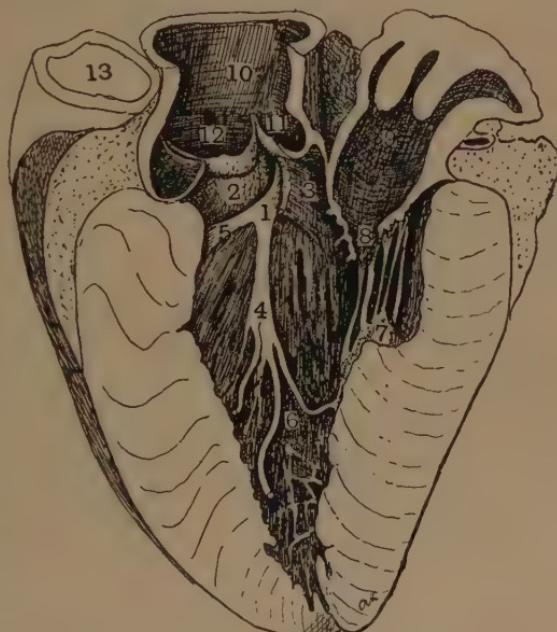


FIG. 258.—Left Ventricle of Calf (Keith and Flack).

1 = Left septal division of A-V. bundle, 2-3 = subaortic musculature divided to show passage of bundle from right side of heart, 4-5 = branches of left septal division passing to (6) moderator bands containing prolongations of bundle to fuse with musculature of heart wall, 6 = left auricle, 7 = aorta, 8 = pulmonary artery, 9 = left auricle, 10 = aorta, 11 and 12 = aortic valves, 13 = pulmonary veins.

If the muscle is still in a refractory condition the wave will stop, but if the wave has travelled at such a speed that the refractory period is finished then the wave may continue passing round the auricle indefinitely. This "circus" movement is responsible for auricular flutter, the production of which is favoured by shorten-

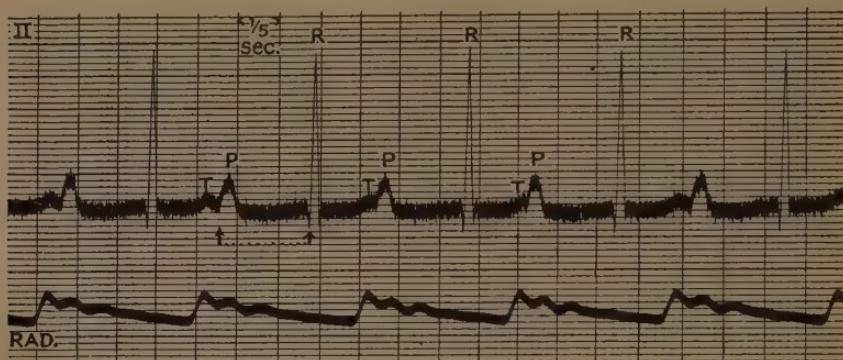


FIG. 259.—Electrocardiogram and Radial Pulse in a Case of Parted Heart-block.

The two arrows show the unusually long interval between the P and R waves of the electrocardiogram. Time marking in  $\frac{1}{5}$  secs. (Kindly lent by Dr. John Parkinson.)

ing of the refractory phase or slowing of the rate of propagation of the contraction wave. Under such circumstances the auriculo-ventricular node will be bombarded by a more frequent series of stimuli, and according to the number to which it can respond the ventricle will beat at a more rapid rate.

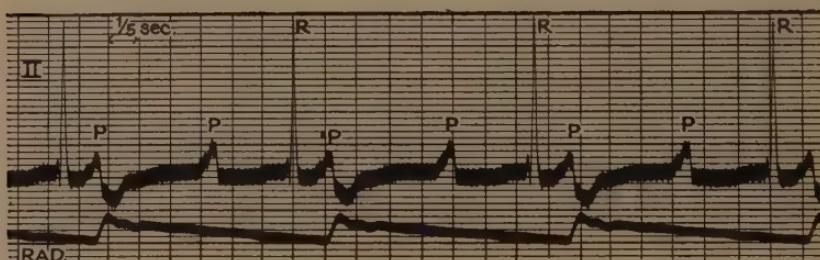


FIG. 260.—Electrocardiogram and Radial Pulse in a Case of Heart-block.

Two P-waves occur before each R-wave and radial pulse (2 : 1 block). Time marking in  $\frac{1}{5}$  secs. (Kindly lent by Dr. John Parkinson.)

A similar "circus" movement has been shown by Mayer in rings of meduse from which the margin of the disc had been removed.

Auricular Fibrillation. A further stage of disorder is that in which the auricle contracts in waves which affect only a few fibres at a time, and the waves pass in a continuous stream from one part

of the auricle to another. This is known as auricular-fibrillation, and for the same reason as the auricular flutter the ventricle beats at a very rapid rate.

*Partial Heart-block.* By interference with the auriculo-ventricular bundle conduction from the auricle to ventricle may be altered. The alteration may be only a slight delay, so that the interval between commencement of contraction of the auricle and commencement of contraction of the ventricle may be prolonged. In other cases the bundle can convey only some of the impulses from auricle to ventricle so that only every second or third auricular contraction will be followed by a ventricular contraction. These interferences with conduction are known as partial heart-block.

*Complete Heart-block.* If the bundle completely fails to conduct, the ventricle beats with its own rhythm independently of the auricle and the condition is known as complete heart-block.

**Output of the Heart.** The output of the heart per minute is the product of the output per beat and the number of beats per minute. Some of the conditions which influence the output of the heart per beat have already been described (p. 64), one of which is the pressure in the venous reservoir formed of the veins between the valves at Poupart's ligament and at the clavicle. The pressure in this reservoir is responsible for the rate of filling of the heart.

With a good flow of blood from the veins the heart is well filled with blood, so that the ventricular muscle is slightly stretched;

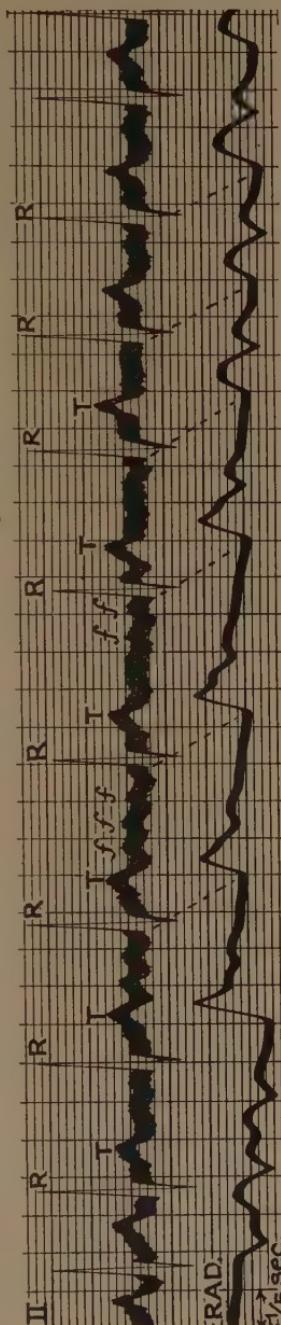


FIG. 261.—Electrocardiogram and Radial Pulse from a Case of Auricular Fibrillation.  
The normal auricular deflection P is absent. Fine fibrillary waves ( $\uparrow\downarrow\cdot\cdot\cdot$ ) occur. The ventricular complexes, therefore the radial beats, are irregular. Time marking in  $\frac{1}{4}$  sec. (Kindly lent by Dr. John Parkinson.)

such stretching causes a more effective contraction (see p. 64). This was shown by Starling and Knowlton, who varied the pressure in the venous supply to a heart-lung preparation (see p. 87).

In the heart-lung preparation the rate of filling of the heart is controlled by the venous reservoir, a greater pressure in which causes more rapid filling of the heart. If the heart is filled more rapidly it will become distended so that the muscle fibres are stretched. Normally the ventricle is slightly distended by the contraction of the auricles, but the auricles are not necessary for normal contraction of the ventricles; they are merely accessory and their function is to aid the filling of the ventricles.

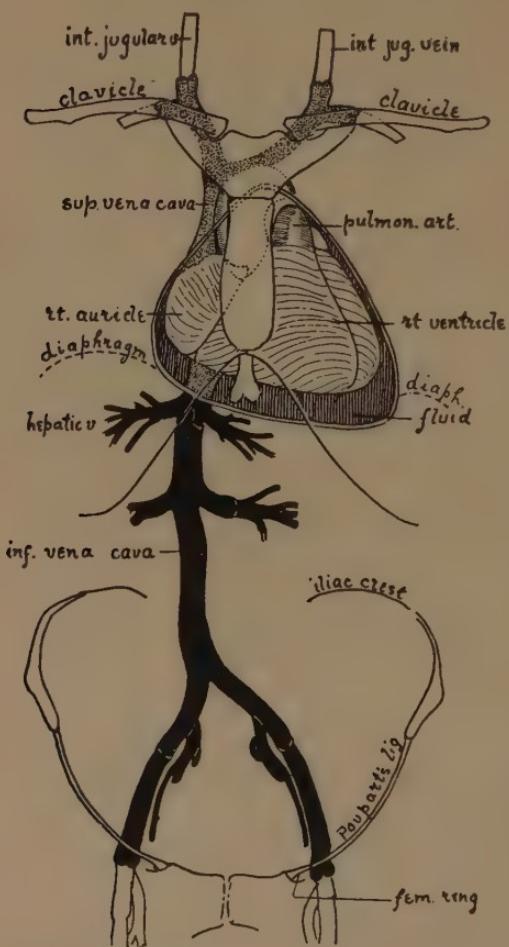


FIG. 262.—Diagram of the Venous Cistern from which the Heart is Filled (Keith).

The abdominal or infra-diaphragmatic part of the cistern is indicated in black; the thoracic or supra-diaphragmatic portion is stippled. The heart is compressed upwards and backwards against its attachments.

really an application of Hooke's Law, namely that the tension in a stretched structure is proportional to the amount of stretching. The volume of blood discharged at each beat can be measured by the cardiometer (see p. 60). It can also be calculated by measuring the total volume of blood discharged which

Stretching the heart muscle causes a more vigorous contraction of the heart. Starling describes this as the *Law of the Heart*, namely that when conditions arise (e.g. a high blood pressure) that prevent the heart emptying completely, the heart responds more vigorously in compensation. This is

divided by the number of beats gives the output per beat.

The total volume of blood passing from the heart may be measured by the heart-lung preparation or by the stromuhr. In man the volume of blood passing through the lungs can be determined from the respiratory exchange. The amounts of gases in blood from the pulmonary artery and aorta (or veins and arteries) can be measured. From this analysis the amount of any gas gained or lost per hundred cubic centimetres of blood can be determined: by dividing this into the total amount of the same gas lost or gained in the lungs the total volume of blood which passed through the lungs, during the experiment, can be estimated. The total amount of blood divided by the number of beats gives a measure of the output of the right ventricle per beat; the left ventricle gives out on the average the same volume of blood as the right ventricle.

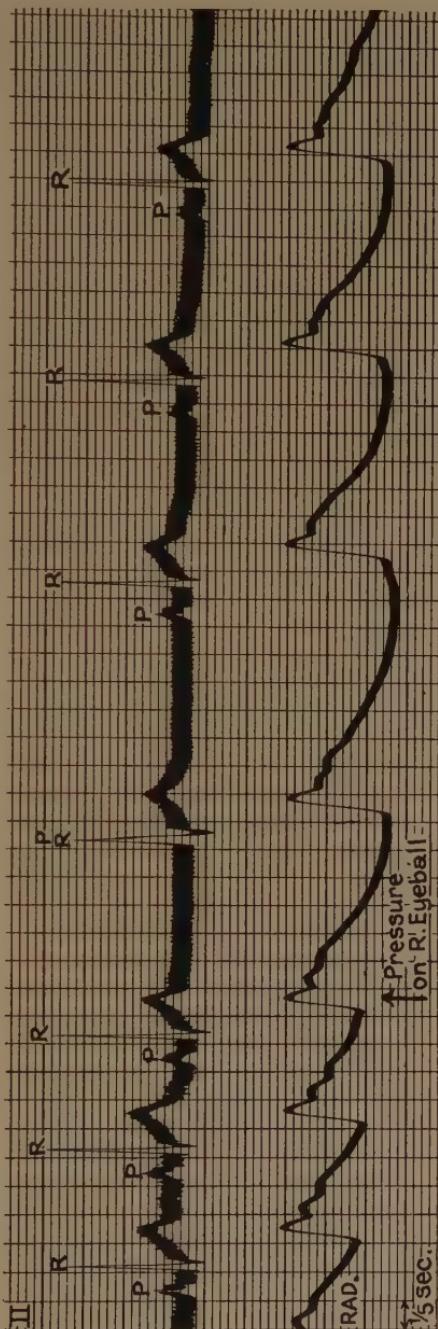


FIG. 263.—Electrocardiogram and Radial Pulse.  
The record shows slowing of a normal heart produced by vagal inhibition as the result of pressure on the eyeball. Time marking in  $\frac{1}{5}$  sec.  
(Kindly lent by Dr. John Parkinson.)

**Rate of Heart Beat.** The number of beats is controlled by nerves ; cutting both vagi causes an increase in heart rate, indicating that the vagi normally exercise a restraining influence on the heart beat. On the other hand, stimulation of the cardiac branches of the sympathetic causes acceleration of the beat. The controlling centre for these two nerves is situated in the medulla and is known as the cardio-inhibitory centre.

**Effect of some Drugs on the Heart Beat.** Pilocarpine applied to the heart causes slowing of its beat and this slowing is ascribed to stimulation of the vagus endings.

Atropine causes increased rate of beat by paralyzing the vagus endings. These two drugs are said to act on nerve endings because they are ineffective before nerve fibres have grown into the heart (Pickering).

Nicotine first stimulates, then paralyzes nerve cells at the synapses, hence it first slows and then causes acceleration of the heart.

In auricular fibrillation digitalis interferes with conduction. The ventricle beats with its own rhythm, or at any rate with a slower beat, therefore improving the circulation because of the longer time allowed for filling the heart, with the result that the output of the heart is increased.

Apart from the influence of the nervous system the rate of the beat depends upon the pacemaker. Warming the sino-auricular node increases the rate of the beat ; cooling it slows the beat.

When the auricle beats more rapidly the ventricle follows it unless heart-block occurs. Thus in auricular fibrillation or flutter the ventricle which requires a certain amount of time to fill with blood becomes inefficient owing to the excessive rapidity of the beat. If ventricular contraction is not preceded by contraction of the auricle it is less efficient because it is less well filled.

**Regulation of the Blood Flow.** The escape of blood from the arteries is regulated by the degree of constriction of the muscular walls of the smaller arterioles. Such constriction helps to counteract the effect of gravity and regulates the supply of blood to the various organs. By dilation of vessels in one locality the blood will escape in that direction, therefore allowing a greater blood flow to active organs by mere dilation of their blood-vessels ; constriction of other blood-vessels will raise or maintain the blood pressure, helping in this way to increase the blood supply of an active organ. The regulation of the blood-vessels is brought about through the involuntary or autonomic nervous system and a centre in the medulla known as the vaso-motor centre.

**Capillary Circulation.** In addition to the resistance to escape of blood from the blood-vessels there is a regulation of the flow in the capillaries. What causes this alteration is not yet known,

but if one observes the capillaries of the frog's tongue, or those under the skin in man, one can see that only a few are visible, that new ones may open up as those previously visible close, or that a larger number may become visible as conducting channels (Krogh).

It is probable that variations in the capillaries may not have much influence on the blood pressure, but the variations depend upon metabolic needs, so that during rest local needs may cause dilation first of one area then of another, so that the small amount of blood flowing is distributed evenly over a definite interval of time, although at any one moment only a few capillaries are being used.

During activity the larger supply of blood from the arterioles is sufficient to cause a flow through many capillaries. If, however, a large capillary area is dilated so much blood may accumulate that there is not enough passed through to fill the veins. As a result the supply of blood to the heart may be insufficient to give an efficient output: the blood pressure falls and fainting may occur in spite of a compensatory quickening of the heart beat.

For this reason we find that the circulation is so regulated that blood is directed to that part where it is most needed and the blood pressure maintained at a sufficient level to force blood up to the brain.

*Histamine* ( $\beta$ -iminazolyl-ethylamine) has the effect of dilating capillaries. Dale and Richards have shown that on injecting it into an anaesthetized cat the blood pressure falls. Although the heart beats vigorously not enough blood is present in the great veins to fill the heart, hence the beat becomes ineffective.

**Control of Capillary Circulation.** The control of the circulation in the capillaries is partly independent of the flow in arteries and veins. Owing to the great curvature of the capillaries tension in its wall need not be very great to balance the pressure in them (see formula, p. 155).

Surrounding the capillaries are branched cells (Rouget cells) which seem able to squeeze the contents out of the capillaries. These cells are regulated so that they respond to mechanical stimulation and also to influences through the nervous system. There seems to be some substance in the blood plasma, possibly the active substance from the posterior lobe of the pituitary, which keeps the capillaries in a state of toxic contraction.

*The nervous control* is exercised partly by means of an axon reflex. If dilute mustard extract be applied to the skin the capillaries dilate. This dilation does not occur if the skin be anaesthetized with cocaine, hence it is not due to direct chemical effect on the capillaries. Further, it is not prevented if the afferent nerves are cut, hence it does not depend on influences reaching the spinal

cord. It is, however, prevented if the nerves are allowed to degenerate (Krogh).

**Depressor Nerve.** In the rabbit an afferent nerve with peripheral endings in the arch of the aorta joins the vagus, but in some other animals this forms part of the vagus throughout its course. Stimulation of the central end of the depressor nerve causes a fall of blood pressure and slowing of the heart beat. If, however, atropine be administered or the cardiac branches of the vagus be cut, the fall of pressure occurs without slowing of the heart-beat.

This fall is brought about by dilation of the arterioles.

The function of this nerve seems to be to relieve excessive blood pressure by slowing the heart beat and dilating the arterioles. The adequate stimulus is apparently the stretching of the arch of the aorta by the high pressure.

Accompanying the fall of blood pressure there is a swelling of the peripheral organs, which can be measured by placing the organ in a plethysmograph (see p. 480).

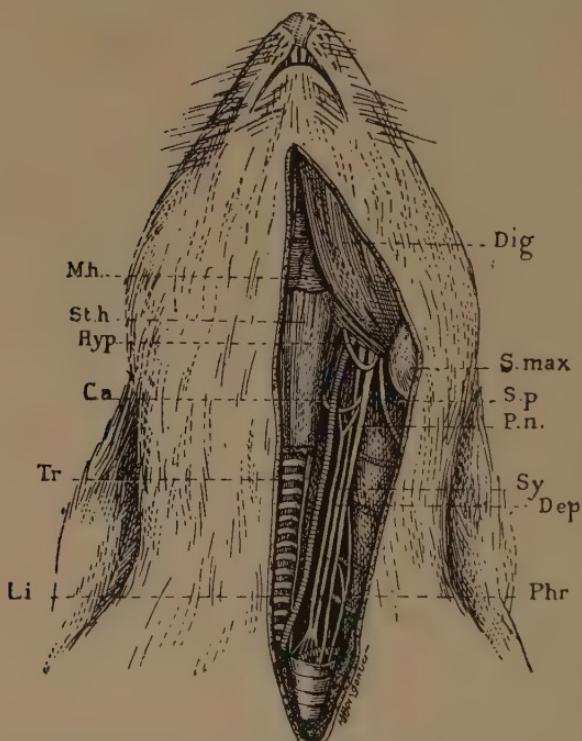


FIG. 264.—Dissection of the Vagus (P.n.), the Depressor (Dep.), and Cervical Sympathetic (Sy.) Nerves in the Rabbit (Cyon).

**Cerebral Circulation.** The circulation in the brain is peculiar because the brain is contained in a rigid case, so that rise in blood pressure can force more blood into the brain only by forcing out something else. The brain substance is incompressible, and the amount of cerebro-spinal fluid is small, therefore any increase in arterial blood supply must be accompanied by a diminution of blood in the venous channels.

The venous sinuses are kept patent by the attachments of dura mater so that they are not obliterated by pressure. An increased

blood flow causes a more rapid current through the narrowed venous channels. Thus it is possible to have a larger amount of blood flowing through the brain by a narrowing of the venous channels.

The intracranial pressure is the same as the pressure in the venous sinuses. If the pressure in the skull is decreased, the sinuses expand and contain more blood, and vice versa. The limit to these reciprocal relations is the attachments of the cerebral sinuses. The reciprocal relationship between the blood flow through the brain and through the other parts of the body can be demonstrated by means of the arm plethysmograph. If some increase in cerebral activity is produced—for instance, by adding up figures—the arm shrinks. This shrinkage shows a constriction of peripheral vessels in order to raise the blood pressure and thus cause a more rapid flow of blood through the brain.

**Circulation in Some Other Parts.** The circulation in the heart is unusual, as the blood must be squeezed out of the intermuscular vessels with each systole. It is doubtful whether there are vaso-motor nerves to either the coronary or cerebral vessels.

The pulmonary circulation is subjected to varying conditions with each inspiration and expiration. There is evidence that the blood-vessels have a vaso-motor supply, but the effect on the blood-vessels is not so striking as in the systemic circulation.

To a certain extent the pulmonary circulation is affected by the systemic circulation and vice versa.

**Acapnia.** Excessive removal of carbon dioxide interferes with the circulation, resulting in a fall of blood pressure with a condition similar to that of surgical shock. This condition of acapnia shows the effect of chemical substances on the centres regulating the blood flow. See p. 457 for the effect of removal of carbon dioxide on the respiration.

**Effect of Respiration on the Circulation.** Frequently respiratory waves are visible on the blood pressure tracing. During inspiration the blood pressure rises and during expiration it falls. This is mainly mechanical in origin because artificial respiration, which reverses the pressure changes in the thorax, inverts the tracing so that there is a fall of blood pressure during the inspiratory movement. There is, however, a nervous element due to decrease in the inhibitory effect of the vagi. The heart beats more quickly during inspiration.

The mechanical factors are due to the decrease in pressure in the thorax and increase in pressure in the abdomen during inspiration. These two factors cause an increased flow of blood to the great veins near the heart with better filling of the right ventricle. A larger output from the right ventricle results in a better filling of

the left ventricle. A greater output from the left ventricle produces a rise in blood pressure.

As it takes a short interval of time for the blood to pass through the lungs the rise and fall of pressure are slightly delayed and are not synchronous with the respiratory movements.

Expansion of the lungs is due to a fall of intrathoracic pressure, which also causes a dilating effect on the blood-vessels. If the blood-vessels expand they will have a larger capacity and allow a freer flow of blood. Part of the delay in the respiratory changes in blood pressure is due to the change in capacity of the blood-vessels.

**Formation and Flow of Lymph.** The problem of lymph formation involves the same principles as the processes described in Chapter XXI. Water diffuses according to the vapour pressure of the solution. Increase in molecular concentration of the solute decreases the vapour pressure with the passage of water towards the more concentrated solution.

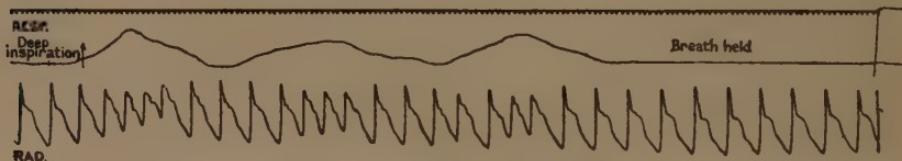


FIG. 265.—Normal Respiratory (Sinus) Arrhythmia, exaggerated by Deep Breathing.

The heart-beat is more frequent during inspiration and less frequent during expiration. When Time marking in  $\frac{1}{2}$  secs. (*Kindly lent by Dr. John Parkinson.*)

In the case of urine filtration we saw that the hydrostatic pressure of the blood was acting against the osmotic pressure of the plasma proteins (Starling). In the capillaries the same forces are present.

The *osmotic pressure* of the proteins is low, but it is peculiarly effective because they do not readily pass through membranes. Solutes which pass easily through membranes cannot produce a permanent osmotic pressure because their concentrations become equal on both sides of the membrane. A temporary effect, however, does occur during the process of equalization.

In the capillaries filtration will occur because the pressure is greater than in the surrounding tissues, but there will be a passage of water in the reverse direction due to the osmotic pressure of the proteins. In the same capillary one of these may be greater at one end of the capillary and the other at the other end. For example, the blood pressure must be greater at the end of the capillary from which the blood is flowing: as the blood passes along the capillary the blood pressure falls, and if filtration has been taking place the concentration of the proteins will be increasing.

At the distal end of the capillary the blood pressure may have fallen to such a value that water will be absorbed, due to the osmotic pressure of the more concentrated proteins.

This simple theoretical statement does not include all the factors of the problem. In the cells metabolites are being formed and they diffuse out towards the capillaries. The metabolites on the average have a smaller molecular weight than the corresponding food substances which pass into the cell. Therefore the molecular concentration will be greater, and although the metabolites can diffuse there will be a gradient of vapour pressure tending to drive water from the capillaries towards the cell. The regulation of this process is not fully understood, but if the regulation is upset fluid accumulates in the tissues, producing oedema.

Normally more fluid leaves the vessels than returns to them. The excess is removed by vessels with muscular coats and valves forming the lymphatic channels. The lymphatics convey the lymph towards the thoracic duct and the right lymphatic duct, so that the fluid is restored to the blood at the junction of the internal jugular and subclavian veins of the left and right side respectively. The lymph is filtered through lymphatic glands where solid particles are separated and perhaps chemical changes may occur also.

In some organs the walls of the blood-vessels are more permeable than in others. Thus the lymph from the liver contains a fair amount of protein. When vessel walls are damaged more protein passes into the lymph.

**Composition of Lymph.** Lymph is alkaline in reaction and contains 6 per cent. of total solids. The composition varies according to the source of the lymph and the activity of the organ from which it is obtained. The following figures from Vierordt's Tables are fairly representative :—

TABLE LVI  
COMPOSITION OF LYMPH

|  |      |           |
|--|------|-----------|
| Water . . . . .                          | 94.0 | per cent. |
| Solids . . . . .                         | 6.0  | "         |
| Fibrinogen . . . . .                     | 0.06 | "         |
| Other Proteins . . . . .                 | 4.26 | "         |
| Fat, cholesterol and lecithin . . . . .  | 0.38 | "         |
| Extractives (soluble in water) . . . . . | 0.57 | "         |
| Salts . . . . .                          | 0.73 | "         |

During absorption of fat from the intestine the lymph from the thoracic duct would contain much more fat than is shown above.

**Effect of Tissue Activity on Lymph Flow.** During activity of an organ the lymph flow is increased. This can be shown either

by analyses of the arterial and venous blood, showing a loss of water, or by measurements of the flow from the lymphatics.

Lymph flow is aided by movements for the same reason that the return of venous blood is aided. Pressure on the lymphatics forces the lymph along and release of the pressure allows the vessels to fill again. Owing to the presence of valves the movement is unidirectional. The muscular walls of the lymphatics may aid in this process. The presence of lymph-hearts in amphibians and birds must not be forgotten in relation to the flow of lymph.

**Relation of Capillary Wall to Lymph Formation.** In the above description it has been assumed that lymph formation is a process which does not involve a transformation of energy potential. Certain substances called lymphagogues are supposed to increase lymph flow by causing a secretory action of the epithelium. Solutions of peptone, extracts of crayfish, mussels or leeches all cause an increased flow of lymph. They are called lymphagogues of the first class. They may act by damaging the capillary wall, and it is not necessary to assume that they cause secretion.

Lymphagogues of the second class, e.g. quantities of such substances as dextrose, urea and sodium chloride, increase lymph flow probably by an increased exchange between the blood and tissues. Although it is not quite clear how this may be brought about, a possible explanation is that the increased concentration of these substances in the blood causes them to diffuse from the capillaries. The increase in molecular concentration of the tissue fluids causes water to pass out of the cells so that the volume of pericellular fluid is increased. The excess of fluid is carried away by the lymphatics.

The amount of liquid in the tissues is governed by the condition of the cells. The permeability of cells and their volume changes are related to the problems of haemolysis. The osmotic pressure of proteins and the effects of inorganic ions such as the hydrogen and hydroxyl ions will have an influence on the water contents in cells.

**Volume of Blood in an Organ and Volume of Blood Flowing through an Organ.** The size of an organ is partly dependent on the amount of blood contained in it. By placing an organ in a closed vessel with rigid walls the change in volume of the organ may be measured by means of a tambour attached to the closed vessel. With each pulse the arteries become filled with blood, and therefore a pulse tracing will be recorded by the tambour. Such an instrument is called a plethysmograph. An interesting form of this instrument is one in which the arm can be placed, and a slow current of illuminating gas passed through it. The issuing gas is lighted and the flame photographed. With each expansion

of the arm more gas comes out and between the beats the gas accumulates in the plethysmograph, and the jet of gas decreases.

Another use of this instrument is the measurement of the amount of blood flowing into the organ. By clamping the vein for a brief interval the swelling of the organ indicates this amount. The plethysmograph is a measure of the volume of blood in the organ and the changes in the amount contained in the organ.

As there is an independent action of the arteries and capillaries we can distinguish the effect of the two. The colour of the organ depends on the state of dilation or contraction of the capillaries. If the capillaries are contracted the blood is forced out of them. If the capillaries are dilated the colour will be pink or bluish, depending on whether the blood is passing through rapidly or stagnating and becoming reduced.

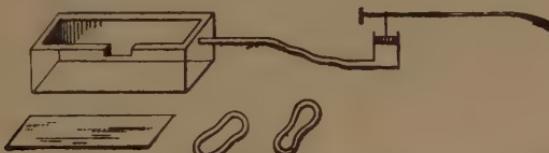


FIG. 266.—Diagram of Plethysmograph and Piston Recorder (Flack and Hill).  
The rubber bands hold the glass lid in position on the box.

The rate of flow will regulate the temperature of an exposed part. If there is a rapid flow through the skin the skin will be warm. One way of measuring this is to place a limb in a calorimeter and measure the rate at which the limb gives off heat.

Thus we find that the circulation is adjusted to the needs of the body of which the most predominant one is the need for oxygen : the supply of food material is not so urgent as local reserves are present. As the limit to oxygen supply is the amount of haemoglobin in the blood, the haemoglobin must be carried round more quickly if a large supply of oxygen is required. During muscular exercise this is brought about by constriction of the splanchnic area, by the pumping action of the muscles on the veins, so that the heart is well filled with blood even with the increase in rate of the heart-beat.

The medullary centres act through the autonomic nervous system, in this way regulating the various parts of the circulatory system.

A blood pressure tracing in addition to pulse and respiration waves frequently shows long period oscillations of pressure which are probably due to variations in activity of the medullary centres (Traube-Hering curves).

NOTE.—For further information the student should consult Bayliss, *The Vaso-Motor System*; Krogh, *Anatomy and Physiology of the Capillaries*.

## CHAPTER XXXV

### INTEGRATION OF DIGESTION AND EXCRETION

#### Digestion

The process of digestion is regulated so that the various stages follow each other in orderly sequence. The various reflex and chemical regulatory processes have been described in Chapters XII to XVI.

In the mouth sensations of taste and smell act as stimuli for the reflex secretion of saliva and of gastric juice. Swallowing also stimulates the flow of gastric juice. The amount of gastric juice regulates the amount of pancreatic secretion because of the formation of secretin by the acid of the gastric juice. Nevertheless, digestion can proceed fairly satisfactorily in the absence of acid in the gastric juice. It may be that fats or fatty acids cause the formation of secretin from prosecretin.

The muscular movements of the alimentary canal are also regulated in the following manner :—

Firstly, the peristaltic movements depend upon the local myenteric plexus of Auerbach between the circular and longitudinal coats of muscle. Painting the excised intestine with cocaine or nicotine stops peristalsis, thus indicating the nervous regulation of the process. Secondly, on removal of the longitudinal muscle from the circular coat Auerbach's plexus adheres to the longitudinal coat, which may show rhythmical contractions if Auerbach's plexus is present, but not if it is absent. For these two reasons it is assumed that peristalsis depends upon the local nerve plexuses. Segmentation, on the other hand, is believed to be a purely local effect due to the distension of the intestinal wall by its contents.

The movements are regulated by extrinsic nerves. The vagi increase the movements of the small intestine, while the sympathetic nerves inhibit the movements. The various sphincters are also regulated—the pyloric sphincter largely by the amount of acid in the stomach and the absence of it in the duodenum, and the ileo-colic sphincter by the degree of distension of the stomach. Thus, shortly after a meal has been taken, contents pass from the small into the large intestine. Normally, the rectum is empty. Relaxation of the circular muscles at the junction of the rectum and the sigmoid flexure of the colon allows some of the contents of

the colon to pass into the rectum, thus arousing the desire for defaecation; this relaxation generally follows a meal.

We do not know how these various events are related. It is tempting to think that the same stimulus associated with filling of the stomach causes relaxation of the ileo-colic sphincter and the circular muscle guarding the rectum. Teleologically, one would expect the small intestine to be emptied in order to be prepared to receive the contents of the stomach, and the large intestine emptied to make room for the contents of the small intestine. This co-ordination might be brought about by nervous processes or by hormones. In the case of the colon some additional factor seems necessary, as in many people defaecation occurs soon after breakfast. This may be a conditioned reflex (see p. 436) due to the habit of

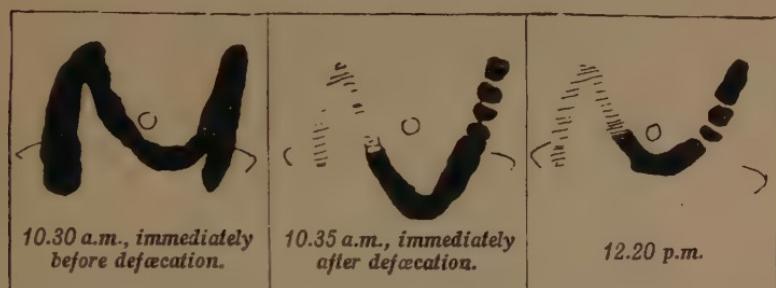


FIG. 267.—Skiagraph of Large Intestine showing Position and Contents of the Bowel Before and After Defaecation (Hurst).

having the bowels opened only once a day, usually after breakfast. Other people may have the evacuation at other times, but it generally takes place soon after a meal.

The experiments of Dodds in which it is shown that secretion of hydrochloric acid is accompanied by a rise in alveolar tension of carbon dioxide suggest a possible hormonal control. An increase in carbon dioxide tension might affect the muscles which guard the openings between the small and large intestine and between the large intestine and the rectum.

The involuntary nerve plexus which controls the intestinal movements are shown in Fig. 268.

Excess of food may cause diarrhoea, but it is not known how this is produced. Nervous diarrhoea is due to the influence of the autonomic nerves.

**Excretion.** The blood is maintained at a fairly uniform composition. It is interesting to note that a substance such as urea, which is regarded as a waste product, may be conserved in some animals. The concentration of urea in human blood is about

0.03 per cent., whilst in some fish the concentration may reach 2-3 per cent., a difference difficult to explain.

Deficiency of the waste product, carbon dioxide, leads to acapnia, a condition in which the circulating system is upset. Regulation of excretion is therefore concerned with maintaining a definite concentration of certain substances in the blood.

The means whereby the concentration of carbon dioxide is regulated has been described (pp. 457-459). Certain substances are excreted by the alimentary canal, but we do not know how this is regulated.

The main excretory organ is the kidney. The physico-chemical processes involved in the formation of urine have been described in Chapter XXI.



FIG. 268.—Photomicrograph of Gold Chloride Preparation of Auerbach's Plexus ( $\times 27$ ).

**Effect of Changes in Pressure.** A rise of blood pressure should lead to increased formation of urine. Closing the renal vein, which ought to cause a rise of pressure in the glomeruli, does not produce a free flow of urine. The reason for the failure of urine formation may be either that lack of oxygen alters the permeability of the membrane or that the blood contained in the capillaries becomes so concentrated after a small quantity of water has filtered through the glomeruli that further filtration is prevented by the osmotic pressure.

Partial blocking of a ureter generally leads to a decreased flow of urine. This decrease is what would be expected if the obstruction caused a rise of pressure in the tubule and Bowman's capsule, which would decrease the difference of pressure between the blood and the contents of Bowman's capsule, and hence cause a decrease in rate of filtration.

**Effect of Changes in Blood Flow.** The blood flow through the kidney depends on the general arterial pressure and the state of contraction or dilation of the renal blood-vessels. A general rise of blood pressure accompanied by constriction of the renal arteries may actually decrease the amount of blood flowing through the kidneys, whilst a fall of blood pressure with dilation of the renal arteries may cause an increased blood flow. Obviously then the most favourable condition for a large blood flow through the kidney is a rise of general blood pressure with a dilation of renal arteries.

The results of experiments show that neither the volume of blood in the kidney nor the pressure are so important as the rate of flow, which may exert its effect by the pressure produced in the glomeruli. When blood is flowing through the glomeruli the pressure of the blood will depend on the state of contraction of the afferent and efferent vessels.

When we attempt to discover the regulating process exercised by the kidney we find it difficult to unravel the various factors concerned.

Drinking large quantities of water leads to the formation of a large amount of extremely dilute urine. This may be due to a decrease in the molecular concentration of the blood leading to a freer filtration through the glomeruli, but such increased formation of urine does not necessarily imply a dilution of the blood.

Regulation of the action of the kidney implies regulation of the action of the glomeruli and of the tubules. If we assume that the glomeruli represent filters we must look to changes in circulation as regulating the flow. The cells of the glomeruli may have a selective action and various physico-chemical processes may alter the permeability of the glomerular membrane. For example perfusion of the frog's kidney with certain solutions containing glucose causes urine formation without sugar in it, but if the calcium salts and bicarbonates are altered in concentration glucose will be found in the glomerular filtrate (Hamburger).

When the afferent vessels are dilated and the efferent are contracted the pressure in the glomeruli will be high, but when the afferent vessels are constricted and the efferent dilated the pressure will be low because such blood as does reach the glomeruli can escape readily by the efferent vessels.

In addition to these effects we must remember that according to Bernoulli's theorem a decrease in the rate of flow will cause a rise of pressure because the kinetic energy is converted into pressure. The large total area of the glomerular tufts will cause a sudden decrease in velocity with a rise of pressure (see p. 77). This conversion of kinetic energy into pressure may help to explain the

influence of the rate of blood flow on urine formation. Constriction of the efferent vessel is necessary, otherwise the blood would escape too rapidly and the kinetic energy would not produce so high a pressure.

The three conditions which co-operate to increase the filtration through the glomeruli are :—

- (1) Dilation of afferent vessels to the glomeruli.
- (2) Constriction of efferent vessels to the glomeruli.
- (3) A free flow of blood.

All these three can be controlled by nerve fibres.

We do not know how the tubules are regulated. Certain substances such as urea have a diuretic effect and at the same time they cause an increased consumption of oxygen. As described on p. 283 this implies some factor in addition to a decrease in potential of one form of energy.

It is quite clear that the total quantity of any substance will not be removed from the blood. If the glomerular filtration is rapid the increase in concentration will be less as the urine passes more rapidly along the tubule. The time of contact of the urine with the tubule cells is one of the factors which exerts an influence on the degree of concentration of the urine.

## CHAPTER XXXVI

### REGULATION OF TEMPERATURE

The temperature of the human body varies during the day by about  $1^{\circ}\text{C}$ .; this variation is ascribed to activity during the day and rest during the night. The highest point is generally about  $37.4^{\circ}\text{C}$ . ( $99.4^{\circ}\text{F}$ .) and the lowest about  $36.3^{\circ}\text{C}$ . ( $97.5^{\circ}\text{F}$ .). The temperature varies with the place where it is measured; the mouth, for instance, may show a low temperature when the face has been exposed to a cold wind. When the temperature is to be measured in the axilla the arm must be kept close to the side for a considerable time, so that the adjacent skin surfaces become warmed to the temperature of the surrounding tissues. The rectum gives the most reliable temperature as it is enclosed within thick protecting layers. By holding the bulb of a thermometer in the stream of urine an accurate measure of the body temperature may be obtained.

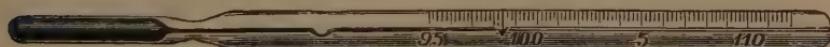


FIG. 269.—Clinical Thermometer.

A clinical thermometer is a maximum one with a relatively small bulb and a narrow capillary which may be magnified by the lens-like shape of the glass wall. In order that the instrument may be read at leisure the stem is constricted and bent so that the mercury does not run back into the bulb until it is shaken down in some way.

Muscular movement raises the body temperature owing to increased oxidation. After strenuous exercise (e.g. after a game of football) the body temperature may be raised and the rectal temperature may register at least  $102^{\circ}\text{F}$ .

In women the menstrual period is associated with a periodic temperature change with a maximum preceding menstruation and a minimum following it.

Apart from these variations the body temperature is maintained at nearly the same value in spite of extremely varying conditions. The external temperature may show wide variations but the body temperature keeps steady. When the external temperature falls there should be an increased heat loss and the body temperature

should fall ; that it does not do so is a testimony to the efficiency of the temperature-regulating mechanism.

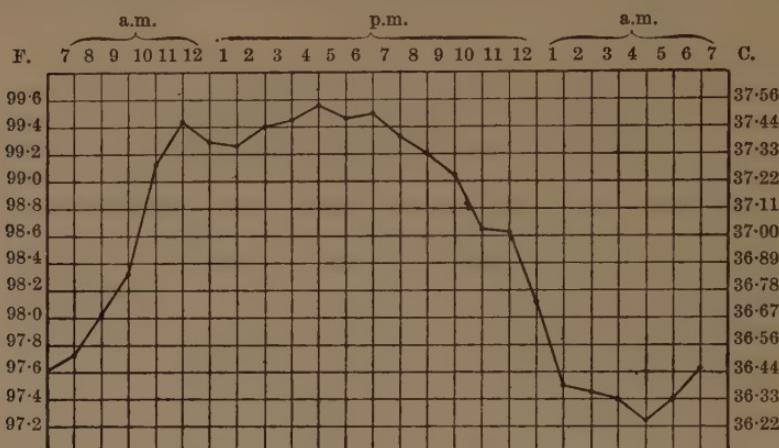


FIG. 270.—Daily Variation of Temperature (Urine) of Man (M. S. Pembrey).

**Heat Loss and its Variation.** The first mechanism to be considered is that of heat loss. This can occur in three ways, namely by radiation, conduction and evaporation. Convection is an additional process whereby the air which has been warmed and moistened by contact with the body is removed so that the difference in temperature and vapour pressure between the body and its surroundings is maintained at a greater difference than if the air stagnated near the body. Convection is due to wind currents and the rising of the lighter air which has been warmed by the body. We may decrease convection currents by houses and by clothing so that the warm moistened air is less rapidly removed, thus decreasing the heat loss. This is merely equivalent to a higher external temperature and the heat loss must be considered mainly as the loss of heat from the body to the layer of air in contact with it.

**Radiation of Heat.** The net loss of heat by radiation and conduction depends upon the difference of temperature between the two objects. Radiation takes place without contact, i.e. between the skin and the walls of the room, etc. As the skin is frequently warmer than the surrounding objects more heat passes from the skin than is absorbed from the surrounding objects, and this exchange is proportional to the difference of temperature. The reverse, however, holds when there is a radiating body at a higher temperature, such as a fire or the sun, then the body gains more heat than it loses.

**Conduction of Heat.** Conduction takes place by direct contact and it is directly proportional to the temperature gradient (i.e. differ-

ence per unit distance) which may be regarded as the difference in temperature between the skin and the layer of air in contact with it. It is by changes in the temperature of the skin that heat loss by conduction is regulated. The skin temperature is lower than the deep or internal temperature. When heat loss from the skin is excessive the arterioles supplying blood to the skin contract and therefore less blood reaches the skin. As the skin is warmed by the blood, the temperature of the skin will fall so that less heat loss will occur. Thus we see that a large blood-flow through the skin means a warmer skin and a greater heat loss. The blood, however, passes back at a lower temperature to be warmed up again, so that the circulation acts as a heat distributor, bringing heat to the skin from the internal organs and passing back to receive another supply of it. The regulation of the heat supply to the skin is brought about by the vaso-motor centre in the medulla.

**Evaporation of Water.** Loss of heat by evaporation depends upon the fact that it requires about 574 calories to convert 1 gramme of water into vapour, and this latent heat is lost from the body by evaporation.

In countries where the temperature is higher than that of the body the conditions described in the two preceding sections are reversed and heat loss can occur only by evaporation.

Evaporation depends on the difference of vapour pressure. The vapour pressure of the air depends on the absolute amount of moisture in the air and is to that extent independent of the temperature, but the temperature has an influence on the amount of moisture which can be held in the air. The saturation values for air are given in Table LVII, from which it can be seen that the air at lower temperatures generally has a lower vapour pressure because excess of moisture is precipitated at these temperatures.

TABLE LVII

PRESURES AND QUANTITIES OF WATER VAPOUR WHEN AIR IS SATURATED WITH MOISTURE (LANDOLT AND BÖRNSTEIN)

| Temperature.<br>Deg. | Pressure (In mm. Hg.)<br>pure water. | Pressure (In mm. Hg.)<br>20 per cent. NaCl. | Quantity (in grams.<br>per litre). |
|----------------------|--------------------------------------|---|------------------------------------|
| 0                    | 4.6                                  | —   | 0.0048                             |
| 5                    | 6.5                                  | —   | 0.0069                             |
| 10                   | 9.2                                  | —   | 0.0094                             |
| 15                   | 12.8                                 | 11.1  | 0.0129                             |
| 20                   | 17.5                                 | 15.2  | 0.0173                             |
| 25                   | 23.7                                 | —   | 0.0231                             |
| 30                   | 31.8                                 | 27.4  | 0.0304                             |
| 35                   | 42.2                                 | —   | 0.0396                             |
| 40                   | 55.3                                 | —   | 0.0512                             |

The vapour pressure of the evaporating surface depends upon the temperature and its "degree of moisture." The effect of

temperature on the vapour pressure of water can be seen in Table LVII. By "degree of moisture" is meant the vapour pressure at the surface compared with the vapour pressure of pure water at the same temperature. An example is given in the third column of Table LVII showing the effect of salt in decreasing the vapour pressure.

There is not yet any direct method of measuring the vapour pressure of the skin. One can of course recognize the differences between a dry skin and a moist skin : in the latter the sweat glands are active. The vapour pressure of the skin depends on the temperature of the skin and on the activity of the sweat glands. The latter are regulated by a centre in the medulla.

**Various Channels of Heat Loss.** The temperature of the body is regulated by a balance of heat production and heat loss. Regulation, however, is only of importance where variation in heat loss can be brought about.—The main regulation is due to the factors described above, but the various channels of loss are given below.

The food and drink taken into the body vary in temperature but the excreta (urine and faeces) are passed at body temperature. Therefore there is a loss or gain according to whether the ingesta bring in less or more heat than is carried away in the excreta. Regulation by this means is carried out only to a limited extent, as by warm drinks and food in cold weather and in collapsed conditions.

The expired air is almost at body temperature and is saturated with moisture. As the inspired air is generally at a lower temperature and contains less moisture, heat is lost in warming the air and saturating it with moisture. Regulation by this means is carried out in animals, such as the dog, by means of panting. Rapid shallow respirations pass a large volume of air through the respiratory passages, whilst owing to the existence of the dead space the amount of pulmonary ventilation is not so increased as to cause excessive loss of carbon dioxide (compare Table XXV, p. 237).

The skin is the main channel of heat loss in the human body and that process has been described in connection with radiation, conduction and evaporation.

TABLE LVIII

RELATIVE IMPORTANCE OF THE VARIOUS CHANNELS OF HEAT LOSS (AT REST)

| <i>Method of Loss.</i>             | <i>Means of Regulation.</i>                     | <i>Amount of Heat Loss.</i> |                  |
|------------------------------------|---|-----------------------------|------------------|
|                                    |   | <i>Large Calories.</i>      | <i>Per cent.</i> |
| Warming food and drink.            | Warm or cool meals                              | 31                          | 1·4              |
| Evaporation from lungs }           | Variations in depth and rapidity of respiration | 256                         | 11·3             |
| Warming inspired air               |   | 4                           | 0·2              |
| Evaporation from skin              | Activity of sweat glands                        | 325                         | 14·4             |
| Radiation and conduction from skin | Vaso-dilation and vaso-con-duction              | 1,646                       | 72·7             |
|                                    | Total   | 2,262                       | 100·0            |

In Table LVIII the data for evaporation from the lungs were obtained by assuming that the inspired air was half saturated at 15° C. and was expired saturated at 35° C. The amount of moisture evaporated from the lungs subtracted from the total amount gives the amount of water evaporated from the skin. The amount of heat lost in warming the air was obtained on the assumption that 500 c.c. of air were breathed at each respiration at 15° C. and expired at 35° C. the number of respirations were averaged at 16 per minute. This amount was subtracted from the total loss by radiation and conduction to determine the heat loss from the skin by these processes.

**Kata-Thermometer** (L. Hill). This instrument was designed to study the effect of atmospheric conditions on heat loss from the body. It is a spirit thermometer with a large bulb which is warmed to above body temperature and allowed to cool. The time that it takes to cool from 100° to 95° F. is noted, i.e. the rate of cooling just above and below body temperature. The time of cooling is determined whilst the bulb is exposed and dry and also when it is covered by a wet cotton cover. Each instrument is standardized and its rate of cooling determined in micro-calories per sq. cm. of surface.

On each instrument is engraved a numerical factor which on division by the time in seconds occupied in cooling from 100° to 95° F. gives the rate of cooling in micro-calories per sq. cm. of surface, that is the rate of cooling = "Factor" / number of seconds occupied in cooling from 100°-95° F. This is the only physical instrument which measures the rate of cooling under conditions approximating to those of heat loss from the body surface. As the skin temperature is variable, an instrument to measure the rate of cooling at skin temperature would not give results which could be compared one with another, hence the adoption of body temperature as that at which the rate of cooling is determined.

The kata-thermometer differs from a wet and dry bulb thermometer in that the measurement is of the rate of cooling, i.e. of a dynamic condition, whilst the wet and dry bulb thermometer measures a steady or static state.

The dry bulb thermometer measures temperature which remains



FIG. 271.—The Kata-Thermometer (L. Hill from the *Phil. Trans. Roy. Soc.*).

the same whether the air is still or moving. The dry kata-thermometer is at a different temperature from the surroundings, therefore the rate at which the air is removed from contact with the thermometer makes a difference to the heat loss.

The wet bulb thermometer measures the balance between the cooling by evaporation and the gain of heat by the cooler thermometer from the surrounding air. As both of these are increased by moving air the wet bulb reading is only slightly altered by convection currents. The wet kata-thermometer, however, is greatly affected by moving air. There is a further difference, namely that the wet and dry bulb thermometers would show the same reading if the air is saturated with moisture, but owing to the fact that the kata-thermometer is usually at a higher temperature than the air the vapour pressure at its surface will be greater than that of the air saturated with moisture and evaporation will still occur increasing the rate of heat loss above that of the dry kata-thermometer.

The dry kata-thermometer measures the heat loss by radiation and conduction, aided by convection. The wet kata-thermometer measures the heat loss by radiation, conduction and evaporation, the two last being aided by convection. Therefore the difference between the two heat losses represents the heat loss by evaporation.

The importance of convection currents for evaporation is shown in the last column of Table LVII. The amount of water vapour which can be contained in one litre of air is so small that evaporation is only of importance when the saturated air is removed from the evaporating surface.

**Variations in Heat Production.** When the external temperature is low the metabolism, as judged by the oxygen intake and carbon dioxide output, is increased. The means by which this increased metabolism is brought about is not entirely clear. There is an increased tendency to movement and movement is accompanied by increased oxidation. Even if movement does not occur oxidation is still increased, and it is ascribed to shivering or to increased tonicity of muscles, but tone as judged by decerebrate rigidity does not cause appreciable increase in oxidation.

The variation of heat production with variations in the external temperature is most marked in animals on a low diet; on a diet with a large calorie value there is a high heat production, as the specific dynamic effect of protein causes an increased metabolism. Unless the animal is storing food substances the quantity absorbed per day must be got rid off. Therefore heat production is largely dependent on the heat value of the diet. Compare for instance the diets used by natives of different climates.

Under these conditions where an excess of heat is being got rid of, external cold may have very little effect on the heat output. A certain amount of heat must be got rid of per day and it is easier to get rid of it when the temperature is lower than when it is high. Thus we see that the effect of low external temperature in increasing metabolism is manifested only when the animal or man is conserving his resources. If necessary an extra amount of material may be oxidized in order to maintain the body temperature. During starvation this extra oxidation causes a more rapid exhaustion of the reserve materials and an earlier collapse of the organism.

Exactly the same may be said concerning muscular exercise. If sufficient exercise is being taken there is no increase in metabolism due to a lower external temperature. It is easier to get rid of the extra amount of heat at a low temperature, but there is no need for increased oxidation to keep the body warm.

Increased heat loss when it does cause increased metabolism increases appetite. By a greater intake of food and increased oxidation the metabolic condition of the body is improved. That seems to be the lesson to be learnt from open-air treatment of disease. When the individual is a suitable case for such treatment increased metabolism and increased food intake seems to tone up the body so that it is in a better condition to deal with bacterial infections.

TABLE LIX

## HEAT PRODUCTION IN SHELTERED AND EXPOSED CONDITIONS (L. HILL)

| Subject. | Calories per min. |           | Increase.<br>Per cent. | Cooling Powers.                   |                                    | Temperature. |           |
|----------|-------------------|-----------|------------------------|-----------------------------------|------------------------------------|--------------|-----------|
|          | Indoors.          | Outdoors. |                        | Dry kato-thermometer.<br>Indoors. | Dry kato-thermometer.<br>Outdoors. | Indoors.     | Outdoors. |
| N. . .   | 1.32              | 1.81      | 38.1                   | 6.5                               | 22.7                               | 54° F.       | 37° F.    |
|          | 1.54              | 1.91      | 26.5                   | 6.7                               | 23.8                               | 52           | 35        |
| M.S. . . | 1.54              | 2.35      | 52.6                   | 6.4                               | 16.9                               | 55           | 41        |
|          | 1.51              | 2.70      | 78.8                   | 8.4                               | 20.5                               | 49           | 35        |
| S.G. . . | 1.21              | 2.20      | 81.8                   | 6.5                               | 18.5                               | 45.5         | 37        |
|          | 1.08              | 1.70      | 57.4                   | 6.3                               | 14.2                               | 58           | 38        |
| L.H. . . | 1.69              | 2.44      | 44.3                   | 6.6                               | 18.1                               | 52.5         | 32        |
|          | 1.87              | 2.32      | 23.5                   | 5.5                               | 21.7                               | 55           | 37        |
| F.T. . . | 1.04              | 1.84      | 76.9                   | 6.1                               | 16.3                               | 54           | 37        |
|          | 1.12              | 1.71      | 52.6                   | —                                 | —                                  | 57           | 43        |
| S.E. . . | 1.20              | 1.74      | 45.0                   | 6.8                               | 16.6                               | 60           | 47.5      |
| I.F. . . | 0.96              | 1.47      | 53.1                   | 6.1                               | 14.2                               | 62           | 54        |

**Nervous Control of Temperature.** Variations in external temperature probably produce their effect by changing the temperature of the blood. Thus cooling the blood passing up by the internal carotids causes increased heat production and the converse also holds good. The control by which these results are produced is exercised by the corpus striatum because local cooling or warming

of that body produces changes in both heat production and heat loss (Barbour).

When heat production is already in excess the regulation is accomplished by altering heat loss, but when heat production is not excessive variations in heat production occur. Local cooling of the corpus striatum by any temperature below 33° C. causes a rise of rectal temperature, shivering and vaso-constriction in the skin. Warming by a temperature above 42° C. causes a fall in rectal temperature, muscular relaxation and vaso-dilation in the skin. The normal regulation will be more delicate than such experimental procedures indicate.

### Functions of the Skin

The great importance of the skin in regulating heat loss leads naturally to a discussion of the functions of the skin. The uses of the skin can be grouped under seven headings.

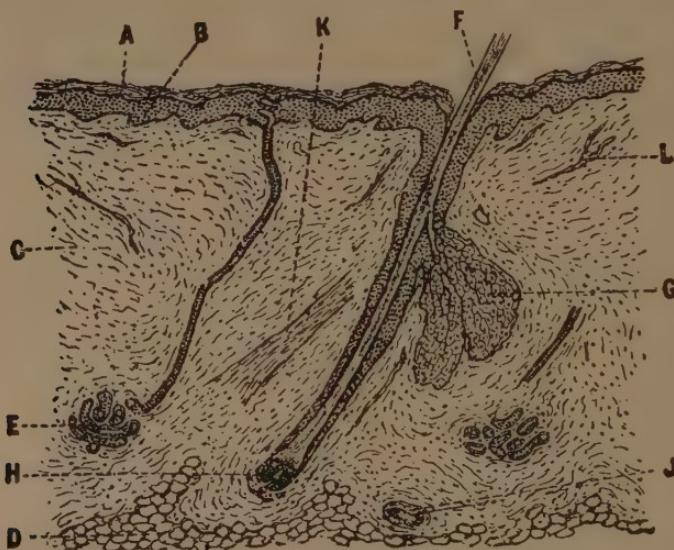


FIG. 272.—Section through Skin as seen under a Low Magnification (L. Hill).

A, Horny layer of cells; B, layers of soft-growing cells; C, thick connective-tissue coat; D, fat layer; E, sweat-gland and duct; F, hair; G, sebaceous gland; H, papilla of hair; I, small artery; K, muscle of hair, L, capillaries.

#### (1) *The Skin forms a Waterproof Envelope.*

If it were not for the presence of a waterproof layer land animals would suffer from excessive loss of moisture. In the absence of the skin the tissues become dried and the cells die. That the skin is perforated by channels which regulate loss of moisture does not detract from the fact that the layer as a whole is waterproof. A

boat does not cease to be watertight because she has pipes by which water may be pumped out of her. On the other hand immersion in water would cause swelling of the tissues if it were not for the protective action of the skin. The sebaceous glands may help in waterproofing the skin by their oily secretion.

The continuity of surface of the skin protects the underlying structure from the entry of micro-organisms.

(2) *The Skin acts as a Mechanical Protection from Violence.*

The hard horny layer which is especially developed on the palm and the sole protects the deeper structures from injury. The loose connective tissue forming the dermis allows the epidermis to move over the deeper tissues. Sliding of the epidermis absorbs the energy of oblique blows so that less strain is put upon the horny layer. This buffer-like action is shown when one compares the effect of a slanting blow with one perpendicular to the skin surface, especially when there is some bony structure close beneath the skin surface.

(3) *The Skin Protects the Body by its Sensory Nerve Endings.*

The sensory endings in the skin by causing reflex or conscious movement remove the body from contact with excessive heat, cold, etc.

(4) *The Skin aids in Regulating the Body Temperature.*

This function has been discussed above. It is brought about by two processes, namely by changes in the amount of blood passing through the skin and by the activity of the sweat glands. It is not the amount of blood actually in the skin but the current through the skin which is important (see p. 481). The activity of the sweat glands is regulated by nerves from the sympathetic system. Stimulation of the sciatic nerve causes secretion of sweat even if the blood-vessels have been clamped before the stimulation occurs. Normally dilation of vessels accompanies secretion, but "cold sweat" shows that the activity of the glands is not entirely dependent on the temperature of the skin. In animals hairs and feathers diminish heat loss. Erection of hairs makes a thicker layer of stagnant air just as putting on thicker clothes decreases the difference in temperature between the skin and the layer of air in contact with it.

(5) *Excretion by the Skin.*

Sweat is an excretion, but it does not appear that its value is great in removal of waste products. A small quantity of urea is present in sweat. Sweat is acid in reaction with a specific gravity of 1005. It contains from 1 to 2 per cent. of solids, of which about 0·7 per cent. is salts. Urea and extractives form a variable quantity.

(6) *Absorption by the Skin.*

Absorption can take place through the skin. This is shown by the appearance of iodine in the urine after it has been painted on the skin. Absorption, however, is not an important function of the skin.

(7) *Respiration by the Skin.*

Respiration is not of any importance in animals with a horny skin. In frogs and animals with similar moist skins respiration through the skin may be an important item in the gas exchange.

Experiments have been carried out in which the skin of an animal was varnished. The animals usually died and it was believed that death was due to stopping of excretion by the skin. It was shown later that the animals did not die if they were kept wrapped in wool and it is now believed that death, which was accompanied by shivering, was due to excessive heat loss by interfering with the functions of the skin.

## CHAPTER XXXVII

### REGULATION OF THE CONCENTRATION OF INORGANIC IONS

#### Regulation of Hydrogen ion Concentration

The reaction of the blood is maintained within a narrow range of values, due to a number of factors, of which the most immediate are the buffers present in the blood (see p. 151); of these the most important is sodium bicarbonate. Addition of acid to the blood causes a combination of the acid with sodium and the setting free of carbonic acid. The carbonic acid by its acidity stimulates the respiratory centre, thus securing its own removal by the lungs. On the other hand addition of alkali causes a retention of carbon dioxide, thus neutralizing the alkali. The mass law equation for these reactions can be written in the form

$$[\text{H}^+] = K[\text{H}_2\text{CO}_3]/[\text{HCO}_3']$$

As the concentration of carbonic acid is proportional to the carbon dioxide tension and the bicarbonate ion is measured by the concentration of bicarbonates multiplied by the degree of ionic dissociation of the bicarbonates, we can rewrite the formula as  $[\text{H}^+] = K_1$  (alveolar tension of  $\text{CO}_2$ )/ $x \times$  (concentration of bicarbonates),  $x$  being approximately 0.8. By this approximate formula we can calculate the acidity by measurement of the alveolar carbon dioxide tension and the total amount of carbon dioxide set free from plasma by acid.

So far as the tissues are concerned the reaction of the blood is the reaction of the plasma. The proteins of plasma have a minor effect as buffers because they are combined with a certain amount of alkali, which can be taken from them by stronger acids.

**Action of Cells on Regulation of Acidity.** The cells of the body also help to regulate the reaction of the blood. Amongst these cells the red blood corpuscles occupy a special position, due to the fact that they are contained in the plasma and that they contain haemoglobin which may exist in an oxy and a reduced form.

The haemoglobin forms a salt with base and the dissociation of haemoglobin can be expressed by an equation similar to that given for carbonic acid :—

$$[\text{H}^+] = K[\text{Hb}]/[\text{Hb}'] = K \text{ [free haemoglobin]}/[\text{salt of haemoglobin}];$$

a corresponding formula holds for oxyhaemoglobin, but in this case K has a higher value. Therefore for the same hydrogen ion concentration more of the haemoglobin will be combined with base when the haemoglobin is in the form of oxyhaemoglobin than when in the form of reduced haemoglobin. Thus when the corpuscles give up oxygen in their passage through the tissue capillaries the base is less firmly united with the haemoglobin with the result that the carbon dioxide from the tissues can combine with alkali from the red blood corpuscles. This means that by loss of oxygen a certain amount of acid may be neutralized without any change in concentration of hydrogen ions.

The exchange between corpuscles and plasma is not however so simple because of the effect of the colloidal constituents of the corpuscle on these exchanges. It has been shown by Donnan that a mixture of the sodium salt of congo red and sodium chloride after dialysis through a parchment paper membrane shows an unequal distribution when equilibrium is reached. Owing to the fact that extra sodium ions are kept inside the membrane by their relation to the congo red less chlorine ions are inside than outside. We cannot go into the explanation of this Donnan equilibrium here beyond stating that the product of the concentrations of sodium and chlorine ions on both sides is equal, so that the excess of sodium inside is balanced by more chlorine outside than inside on

$$[\text{Na}_i^+][\text{Cl}_i^-] = [\text{Na}_o^+][\text{Cl}_o^-]$$

where *i* and *o* are used to indicate the concentrations of the ions on opposite sides of the membrane. Applying these considerations to haemoglobin we see that oxyhaemoglobin, by forming a salt with cations (mainly potassium), will cause a redistribution of anions so that more anions will be outside the cell than when the haemoglobin is reduced. The increase in anions is mainly due to bicarbonate ions, and it is to be noted that there is an actual decrease in chlorine ions in the plasma of venous blood as contrasted with arterial blood.

The full explanation of these facts is not yet known, but they may ultimately be explained on the basis of the unequal distribution due to a Donnan equilibrium. The fact remains, however, that addition of carbon dioxide to blood causes an increase in the bicarbonate of the plasma with a decrease in the chloride of the plasma. It has been stated that bases do not pass through the corpuscle wall and therefore the exchange of anions must occur.

A further consequence of the Donnan equilibrium is that the hydrogen ion concentration inside cells need not be the same as that of the plasma or lymph and that we do not know what the reaction of cells really is.

This exchange between cells and their surroundings is a second factor in regulating the reaction of the blood.

**Influence of Metabolism on Reaction of the Blood.** When the blood becomes more acid the reaction whereby ammonium carbonate is converted into urea is inhibited. Thus the alkaline ammonia neutralizes the acids instead of being converted into the neutral urea. The ammonia in the urine may be formed by the kidney and not transferred to the kidney in the blood. In any case, however, the excretion of ammonia means the saving of fixed bases in the body. Similarly the conversion of alanine into the more acid lactic acid is inhibited by acid (Dakin and Dudley).

On the other hand increase in alkali leads to increased formation of urea from ammonia, to increased production of acids such as lactic,  $\beta$ -hydroxybutyric and aceto-acetic acids and to retention of carbon dioxide.

Therefore a third factor in influencing the reaction of the blood is alteration in metabolism, whereby change of reaction is minimized.

**Influence of Excretion on Reaction of the Blood.** We have seen above that excretion of carbon dioxide is one of the factors in regulating blood reaction, but in addition excretion by the kidney also has a regulating action.

Human urine is generally acid in reaction due to a preponderance of acid phosphate over alkaline phosphate. A change of blood reaction changes the ratio of acid to alkaline phosphate. Thus comparatively large quantities of acid may be removed without a great change in reaction of the urine as the phosphates form a buffer system. The removal of alkali can be aided by excreting it as bicarbonates: thus the alkaline urine of herbivora contains bicarbonates in addition to an excess of alkaline phosphates. After excretion such urine becomes more alkaline by escape of carbon dioxide so that the bicarbonates become partly converted into carbonates.

The carbon dioxide tension of urine is approximately the same as that of the alveolar air, but in acid urine the *quantity* of dissolved carbon dioxide is small, therefore in alkaline urine the escape of carbon dioxide has a relatively greater effect on the reaction of the urine.

By excretion of urine more acid than the blood a saving in base is accomplished. Weak acids are partly present in the form of free acid, the amount of which depends upon the concentration of hydrogen ions and the magnitude of the dissociation constant.

Phosphoric acid is a special case of such a weak acid because the  $H_2PO_4^-$  ion dissociates as a weak acid. Therefore the amount of base saved by the excretion of acid phosphate is the difference

between the molecular concentration of acid phosphate in the urine and the corresponding amount of alkaline phosphate at a reaction equal to that of the blood plasma. On the other hand excretion of urine more alkaline than the blood means a saving of fixed acids, because bicarbonates carry away a certain amount of base without the corresponding quantity of fixed acid.

The regulation of reaction of the blood depends on four factors. 1. The buffers of the plasma. 2. The exchanges between the cells and their surrounding fluids. 3. Alterations in metabolism, and 4. Excretion of excess of either acid or alkali. These factors are given in the order of rapidity in which they act, but the quantitative effect of their activity is probably in the reverse order. For instance the buffer value of the blood is limited, but the ability of the kidney to excrete excess of acid or of alkali is practically unlimited.

The following definitions are useful in describing the effect of various conditions on the reaction of blood.

*Reaction of blood* means the hydrogen ion concentration of blood plasma.

*Titratable alkali* means the amount of alkali combined with weak acids. It is measured by titrating the plasma with standard acid, using an indicator. As the end point will vary with the indicator used the final hydrogen ion concentration to which the plasma is titrated must be stated for a comparative series of measurements.

*Bicarbonate content or alkali reserve.* This is the amount of carbon dioxide combined with alkali in the form of bicarbonates. It is determined by measuring the volume of carbon dioxide set free from one hundred volumes of blood (or plasma) which has been in equilibrium with alveolar air. The amount of carbon dioxide in physical solution is subtracted from the total amount obtained so that the result indicates the combined carbon dioxide.

*Ketosis* means an excess of the products of partial oxidation of fatty acids.  $\beta$ -hydroxy-butyric acid is not a ketone but aceto-acetic acid and acetone are ketones. These three are the substances which are found in ketosis.

*Carbon dioxide pressure* is the partial pressure of carbon dioxide in equilibrium with the plasma. By measurement of this value the amount of carbon dioxide in physical solution is determined and that value indicates the amount of free carbonic acid in the solution.

Variations in the blood may be due to variations in these various substances. *Acidæmia* is used to designate an increase in the concentration of hydrogen ions and *alkalæmia* means a decrease in the concentration of hydrogen ions in the blood plasma.

There may be a change in concentration of carbonic acid without

a change in hydrogen ion concentration. By the equation on p. 497 this will occur if there is a corresponding change in the concentration of bicarbonate ions. Conversely a change in bicarbonate content will not cause a change in hydrogen ion concentration if the pressure of carbon dioxide changes in the same proportion.

Ketosis by neutralizing base diminishes the amount of bicarbonate, hence in order to keep the hydrogen ion concentration near its normal value there must be a fall in the alveolar pressure of carbon dioxide. Excess production of lactic acid will cause in a similar way a fall of carbon dioxide pressure in the alveolar air. Dodds finds that removal of acid from the blood by the stomach causes a rise in alveolar carbon dioxide pressure which would be the natural result of the increased amount of base left in the blood if the hydrogen ion concentration is to remain constant. The reverse occurs during the secretion of alkali by the pancreas.

The conditions in the blood cause compensatory changes in the urine. The alkaline tide (Bence Jones) is an increase in alkalinity of the urine, believed to be the result of the alkali left when hydrochloric acid is removed by the stomach. Ketosis will cause a large amount of  $\beta$ -hydroxy-butyric, and aceto-acetic acids and acetone to be excreted in the urine.

### Regulation of the Concentration of other Ions

Although the ratio of hydrogen to hydroxyl ions is of great importance it must not be overlooked that other ions are also important. The concentration of the salt in blood remains fairly uniform in spite of variations in daily intake. In the case of inorganic substances the regulation of their concentrations in the blood must be brought about by the intestine and kidney. We do not know to what extent the concentration of salts absorbed into the blood may be regulated by the small intestine, but we do know that certain substances such as iron, calcium and magnesium are excreted by the large intestine. The main regulation is undoubtedly exercised by the kidney, but we do not know whether this is a local action by the kidney or if it is regulated by nervous influences.

Small amounts of sulphate and phosphate ions are formed during the oxidation of sulphur and phosphorus containing proteins and lipoids.

There is, however, no doubt that the concentrations of the various ions affect the physiological activities of tissues. The influence of the various ions in Ringer's Solution on the heart-beat may be quoted as showing how important the inorganic constituents are in relation to the tissues.

There are sufficient amounts of inorganic constituents in tissues

to enable one to go without salts for some time. Such stores merely serve the same purpose as buffers in minimizing changes in concentration, but they are limited in amount.

In the case of hydrogen and other ions we do not know how the concentration is regulated. In the case of the former we know that the respiratory centre and kidney are the most important channels of excretion.

## CHAPTER XXXVIII

### —INTEGRATION OF METABOLISM—

The normal metabolism is dependent upon the normal functioning of a large series of organs which are described under the term ductless glands or endocrine organs. They consist of Thyroid and Parathyroids, Adrenals, Pituitary gland, Thymus, Pancreas, Testes and Ovaries.

All cells form substances which may affect the activity of other organs, but it is only in special cases that we regard the cells as forming a chemical messenger or hormone. Thus, carbon dioxide and urea which stimulate the respiratory centre and kidney respectively, are waste products and are not classified as hormones. The chemical substances may not pass directly into the blood, as they can reach it by the lymph, but it is significant that the endocrine organs have a very rich blood supply.

**Thyroid and Parathyroid Glands.** These two different kinds of glands are derived from the branchial clefts. The thyroid is an evagination from the floor of the mouth, and the parathyroids grow from dorsal aspects of the third and fourth gill clefts. At one time they were believed to be all one structure, and that after removal of the thyroid the parathyroids developed to take the place of the thyroid. The colloid developed in the parathyroids is not, however, comparable to that in the thyroid and it is now believed that they perform different functions.

The early attempts at removal of the thyroid were usually followed by death of the animals, but it is now known that death was due to removal of the parathyroids more than to removal of the thyroid. As the parathyroids are closely associated with the thyroid special care must be taken if one wishes to remove the thyroid without removal of the parathyroids.

*The thyroid* is formed of a number of vesicles containing an evenly staining homogeneous material called colloid. The vesicles are lined by cubical epithelial cells supported on a basement membrane. Between the vesicles is connective tissue containing blood-vessels. The colloid differs from all other substances in the body, because it contains appreciable quantities of iodine.

The function of the thyroid, like that of the other endocrine organs, has been discovered by a combination of methods which are : (1) Observation of the effects of disease ; (2) the result of surgical removal ; (3) the histological structure of the organ ;

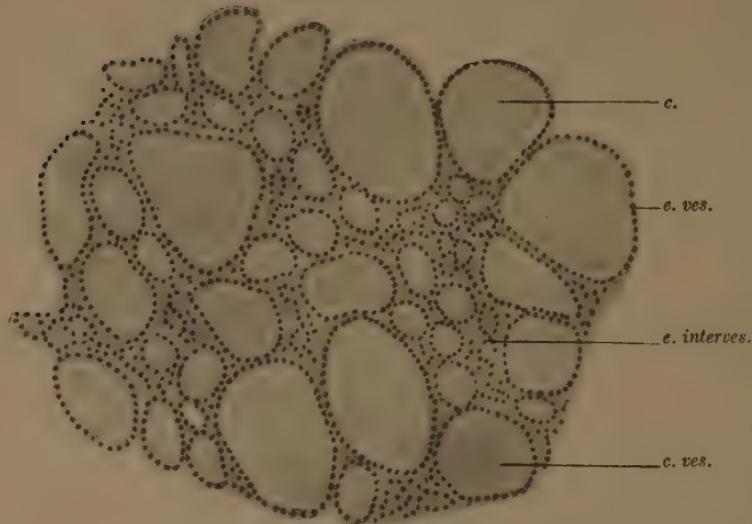


FIG. 273.—Thyroid of a Normal Dog.

c., colloid; e. ves., epithelium lining vesicles; e. interves., epithelial intervesicular tissue; c. ves., colloid vesicle ( $\times 120$ ) (from Swale Vincent).

(4) the effect of administration of extracts from them or its actual feeding on the organ itself; (5) the result of implantation or



FIG. 274.—Photograph of Twin Lambs, both Female.

The one to the right had the thyroid removed at the age of one month. The one to the left is the control. Photograph taken at age of one year and seven months. The dejected attitude of the cretin is characteristic. (Photograph kindly lent by Professor Sutherland Simpson.)

grafting; (6) the action of extracts from them on isolated organs.

The first observation was that the swelling of the gland (goitre) in children was associated with a condition of cretinism, a condition characterized by failure of growth and mental development. In the adult, goitre was often associated with myxœdema, a disease marked by mental inertia and swelling of the subcutaneous connective tissue.

Enlargement of the gland might be due to an over-development of the active glandular material, or a lack of activity; in the case of myxœdema and cretinism the enlargement is accompanied by the latter.



FIG. 275.—Effect of Thyroid Treatment on Cretinism (Hertoghe in *The Practitioner*).  
The figures show the effect of 1, 2 and 3 years' treatment: total growth  $13\frac{1}{2}$ ".

Removal of the glands produces symptoms corresponding to cretinism and myxœdema, depending on the age at which the thyroid is removed. The early experiments were usually complicated by removal of the parathyroids, as mentioned above.

The symptoms of decreased activity on removal of the thyroid are decreased rate of metabolism and interference with growth and activity both physical and mental; for instance, the skin becomes dry and cold, and the hair falls out. Figs. 275 and 276 show the typical appearance due to decreased thyroid activity. These symptoms, whether due to disease or operative removal, disappear when the gland is grafted in another situation, or if the active material is given by the mouth or an extract is injected subcutaneously, provided that the lack of thyroid has not existed for too long a time.

Excessive doses of thyroid produce a series of symptoms of rapid

heart-beat, unstable nervous system, protrusion of eyeballs, flushing of the skin and increased perspiration, and a disease with similar symptoms accompanied by swelling of the thyroid is known as exophthalmic goitre. Thus there appears to be swelling of the gland with deficient activity and swelling of the gland with excessive activity.

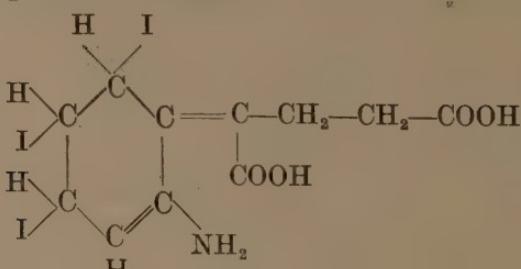


FIG. 276.—Effect of Thyroid Treatment on Severe Advanced Myxœdema (Hertoghe in *The Practitioner*).

The initial weight was 15 st. 11 lb. At the end of a two months' course of treatment with thyroid, he had lost 43 lb., 20 per cent. of his initial weight.

sugar is also affected; thus decreased thyroid activity diminishes the ease with which glycosuria may be produced, whilst excessive activity causes a disappearance of stored carbohydrate.

The action of the thyroid is associated with the presence of iodine in it. Various attempts have been made to isolate the active substance, and the activity has been ascribed to Iodothyro-globulin, Iodothyron and Thyroxin. The first is an impure active substance of a protein nature. The second is not of constant composition, and the third is a crystalline substance which acts on metabolism in the same way as thyroid extract. Thyroxin is a tri-iodo derivative of tryptophane, and the following formula is one of three possible forms :—



Thyroxin.

Further evidence on this subject is given by observations on metabolism. If the oxygen intake is measured, when the body is at rest, and some hours after a meal (post-absorptive state), the energy expenditure is at a low level: this is called the basal metabolism. In healthy individuals the value varies about the value of forty calories per sq. metre of body surface per hour. If thyroid activity is deficient the oxygen intake is decreased, or if it is excessive the oxygen intake is increased. The metabolism of

It is probably a derivative of tryptophane, and the two other formulæ consist of the indol ring being closed between the NH<sub>2</sub> and COOH groups with an enolic and ketone group respectively in the place of the COOH group.

This substance is found to have the properties of an active thyroid gland. Therefore, administration of thyroxin can improve the condition of a cretin or a person suffering from myxœdema.

The thyroid exercises its influence by its action on metabolism, but we do not know how this effect is brought about. As the formula for thyroxin shows that iodine is necessary for the formation of the active substance, deficiency of iodine in the diet may be a limiting factor for the activity of the thyroid under some circumstances. The resemblance of the structural formula of thyroxin to that of tryptophane suggests that there may be some relationship between these two substances, but no experimental evidence is available to indicate that deficiency of tryptophane has any influence on the activity of the thyroid gland.

The gland shows physiological variations in size; it increases at puberty, during menstruation and pregnancy. The increase in size at puberty may become pathological. In some countries where goître is frequent, treatment of adolescent girls with small doses of potassium iodide is believed to diminish the number of cases of goître which develop. It is not impossible that part of the therapeutic value of iodides as alteratives may be due to an effect exercised through the thyroid gland.

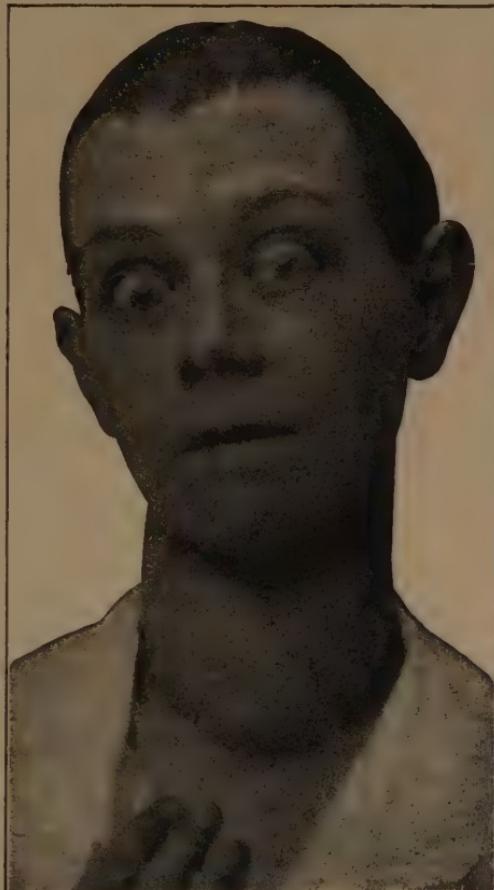


FIG. 277.—Exophthalmic Goître (from Adami).

*The Parathyroids.* As stated above, these organs have a function apart from the thyroid. Their structure is different, consisting of masses of epithelial cells. These polygonal cells are divided by connective tissue septa into masses and cords of varying sizes and shapes.



FIG. 278.—Semi-diagrammatic Sketch showing the Position of the Parathyroids, the Thyroid, and the Trachea in the Human Subject.

Front view. Parathyroids projected on to the surface (from Swale Vincent).

Removal of the parathyroids causes death preceded by muscular twitchings. This condition of irregular muscle contractions and increased irritability to electrical stimulation is known as tetany. Tetany can be produced by injections of guanidine and the muscular twitchings can be alleviated by injection of calcium salts.

The functions of ductless glands may consist in removal and alteration of poisonous substances from the blood, or the addition of something required for the normal action of other tissues. There is no reason why removal of a toxic substance may not be accompanied by its transformation into a useful substance.

In the case of the thyroid we have an instance of a substance

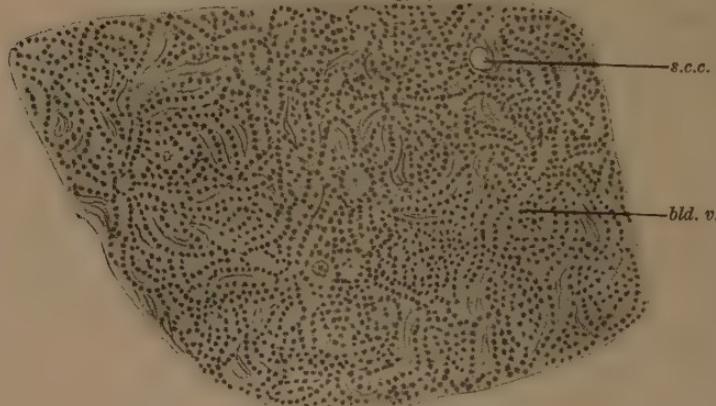


FIG. 279.—Parathyroid of a Normal Dog ( $\times 120$ ).  
s.c.c., solid columns of cells; bld. v., blood-vessel (from Swale Vincent).

which was of use to the body. In the case of the parathyroid we have an organ which may be concerned with removal of guanidine, rendering it non-toxic : there is also the possibility that the parathyroid is concerned with the regulation of calcium metabolism.

**The Adrenals.** In 1849 Addison described the disease now called after him which he found to be associated with destructive disease of the adrenal bodies. The main symptoms are muscular



FIG. 280.—Section through portion of the Adrenal Body of a Dog, showing the various Zones of the Cortex, and the Medulla (from Swale Vincent).

c., capsule; m., medulla; z.f., zona fasciculata; z.g., zona glomerulosa (zona arcuata); z.r., zona reticularis.

weakness, low blood pressure, attacks of diarrhoea and vomiting and pigmentation of the skin, especially where exposed to irritation by pressure, rubbing or sunlight.

Removal of adrenals usually causes death, with symptoms of muscular weakness, low blood pressure and dyspnoeic respiration, but pigmentation does not occur, owing to the short time that elapses before death occurs.

Like the thyroid and parathyroid the adrenals consist of two distinct structures, cortex and medulla. The cortex is derived from the coelomic epithelium, and consists of cubical cells arranged in three different layers. The zona glomerulosa, lying directly under the connective tissue capsule, shows cells arranged in arches, hence the name ; the zona fasciculata, consisting of parallel rows

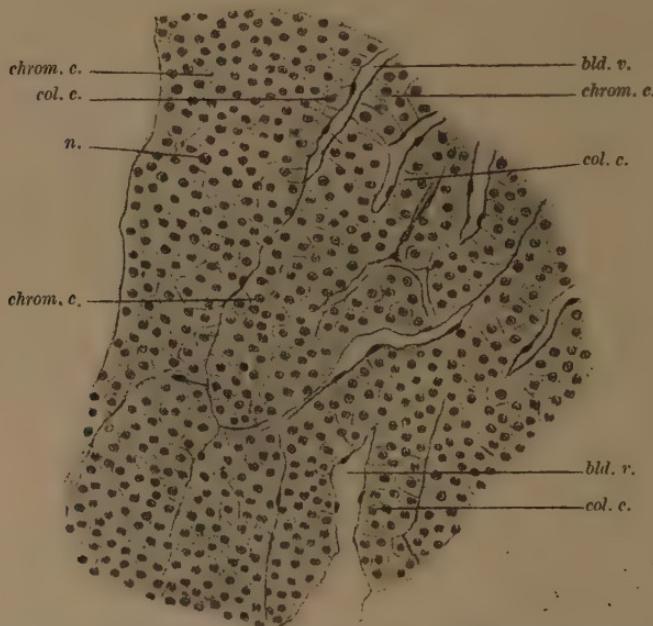


FIG. 281.—Section through the Medulla of the Adrenal of a Dog.  
*bld. v.* = blood-vessels, *chrom. c.* = chromaphil cells, *col. c.* = columnar cells of adrenal medulla,  
*n.* = nuclei (Swale Vincent).

of cells ; and the zona reticularis, which shows cells arranged in an open network of cell columns. The medulla is developed from sympathetic nerve cells which become invaginated into the cortical portion. It is characterized by irregular-shaped cells, which stain brown when the organ has been fixed in solutions containing bichromates, and which form what is called chromaffin tissue. Both cortex and medulla are plentifully supplied by blood-vessels.

The functions of the two parts may be separate, as suggested by their different origin and structure and by the fact that they exist as separate structures in fishes ; but the association of them



A.      Injection of Adrenalin.

B.      Cessation of stimulation of nerves to thyroid.

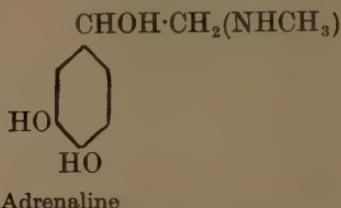
FIG. 282.—Effect of Injection of Adrenalin on Arterial Blood Pressure (Asher and Flack).

*A* = effect of injection of adrenalin. *B* = effect of injection of a second dose of the same quantity of adrenalin with concomitant stimulation of nerves to thyroid. Note that the rise of blood pressure is greater, whilst usually a second dose of adrenalin has less effect than the primary dose.

in higher animals suggests that there is some co-operation between them.

The discovery in 1895 by Schäfer and Oliver that extracts from

the adrenals cause a marked rise in blood pressure led to a rapid increase in the knowledge of the action of such extracts. It has been established that the chromaffin tissue is responsible for the substance that produces the rise in blood pressure, and a crystalline compound known as adrenaline has been isolated from the adrenals. The formula of this substance is



*Adrenaline.* This substance has been synthetized and its physiological effects studied.

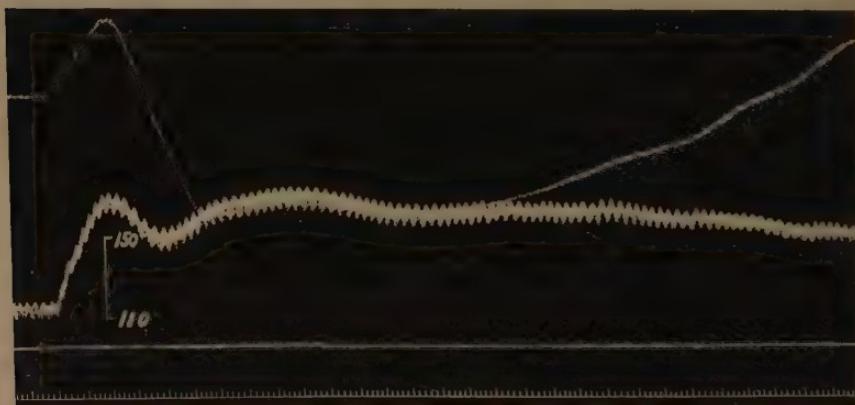


FIG. 283.—Effect of Stimulating the Peripheral End of the cut right Splanchnic Nerve. Dog under Ether, Morphine and Curare with both vagi cut.

Upper curve = volume of denervated limb. Lower curve = carotid blood pressure. Time marking in secs. (Swale Vincent).

In addition to producing a transient rise of blood pressure it produces effects corresponding to stimulation of sympathetic nerves, and this sympathomimetic action (Barger and Bale) is produced by many allied substances. The action is due to the substituted amine group, intensified by the hydroxyl groups on the benzene ring and by the asymmetric carbon atom attached to the ring. In fact, the dextro-rotary compound is relatively inactive, whilst the lævo-rotary compound is active, hence the racemic synthetic adrenaline has about half the activity of the lævo-rotary adrenaline obtained from natural sources.

The physiological problem is to determine the rôle that adrenaline plays in normal metabolism. Adrenaline raises the blood pressure

and increases the amount of sugar in the blood : it thus puts the organism in a condition favourable to muscular action. Stimulation of the splanchnic nerves causes a rise of blood pressure which shows a double crest. The first crest is due to direct constriction of the abdominal blood-vessels : the second is due to general vaso-constriction from adrenalin, as it is not present if the nerves to the adrenals are cut, or if the blood flow from the adrenals is stopped. Further, as shown in Figs. 283 and 284, the first rise of blood pressure is accompanied by a passive dilation of peripheral blood-vessels, whilst the second rise is accompanied by a constriction.

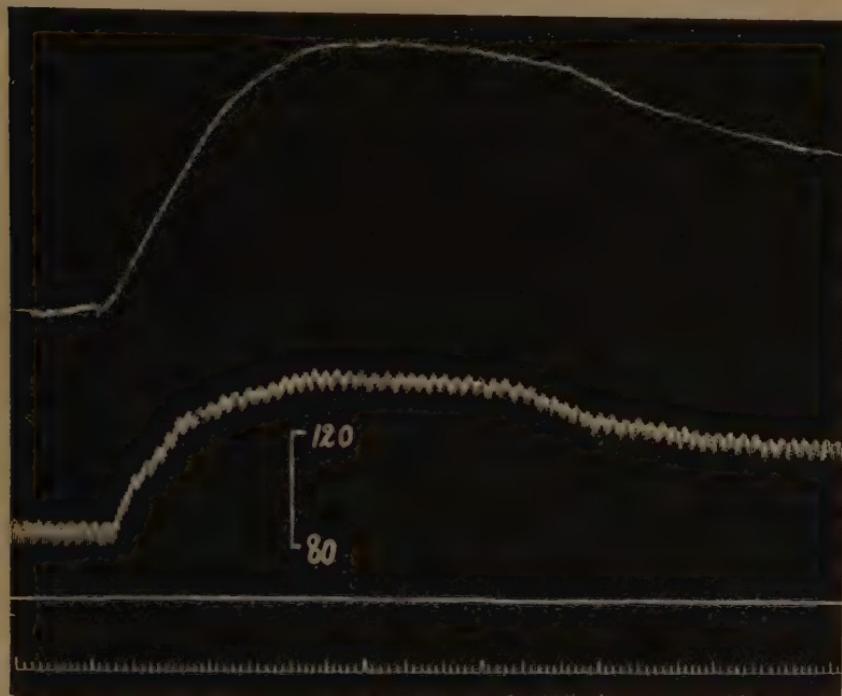


FIG. 284.—Experimental Details as in Fig. 283, but after Adrenal Veins had been Clamped on both Sides (Swale Vincent).

Adrenalin does not stimulate the sweat glands although from its sympathomimetic action one would expect it to do so. It produces acceleration of the heart and its effect on the uterus varies with the species of animal and with its sexual condition : in some animals (e.g. cat) it causes relaxation of the uterus in the non-pregnant and contraction in the pregnant condition. It has no effect when given by the mouth as it is destroyed in the alimentary canal.

Cannon found that by producing emotion in cats there was

evidence of the discharge of adrenalin which is thus preparing the animal for flight or fighting. The rapid heart-beat of excitement is familiar to us all, and it may be due to extra discharge of adrenalin preparatory to increased muscular activity.

Cutting the splanchnic nerves stops the discharge of adrenalin during emotion. Thus if the splanchnic of one side is cut and the animal killed after it has been excited to show emotion, the adrenal of the side on which the nerve has been cut is said to contain more adrenalin than the side to which the nerve supply was intact, but this result is not accepted as fully established.

The fall of blood pressure which frequently separates the two crests on the blood pressure tracing may be due to the effect of adrenalin, which in small doses causes a fall of pressure. The fall of pressure would be succeeded by a rise as the amount of adrenalin increased in amount.

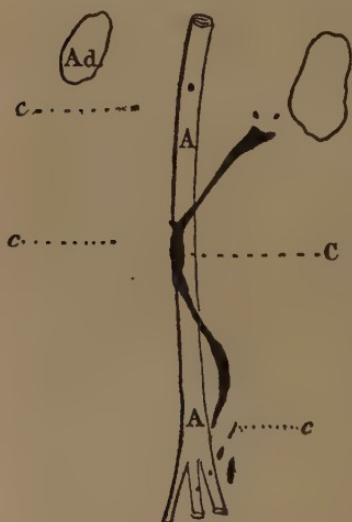


FIG. 285.—Abdominal Chromaffin Body of an Adult Dog.

A = aorta, Ad. = adrenal, C = abdominal chromaffin body, c = smaller chromaffin bodies (from Swale Vincent).

to life. Removal of the whole adrenal, of course, removes the medulla as well, but as chromaffin tissue is found lying on the posterior abdominal wall (dogs), removal of that portion in the medulla is probably not the cause of death.

Tumours of the adrenal cortex are associated with premature or excessive sexual development. The function of stimulating sexual activity is in agreement with the origin of the cortex from the coelomic epithelium.

**Pituitary Body.** This organ consists of three parts—anterior, posterior and intermediate. The anterior and intermediate parts are separated by a cleft, and the anterior part grows round the sides so as to enclose the intermediate and posterior portions.

Another means of showing that adrenalin is set free in the blood during emotional disturbance is by the "paradoxical pupil effect." When the superior cervical ganglion has been removed dilation of the ipsilateral pupil occurs on subcutaneous injection of adrenalin, whereas a similar injection has no effect on the pupil of a normal mammal. Therefore dilation of the pupil on the operated side may be interpreted as a liberation of adrenalin due to the emotional disturbance.

The cortex seems to be essential

The anterior part is developed from Rathke's pouch at the back

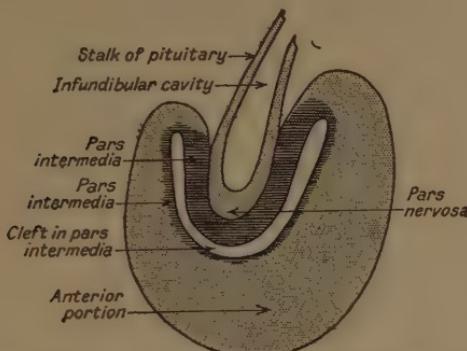


FIG. 286.—Diagram showing Relation of Principal Parts of Pituitary Body (from Swale Vincent).

of the naso-pharynx ; it consists of cubical epithelial cells, arranged in branching columns, which vary greatly in their intensity of

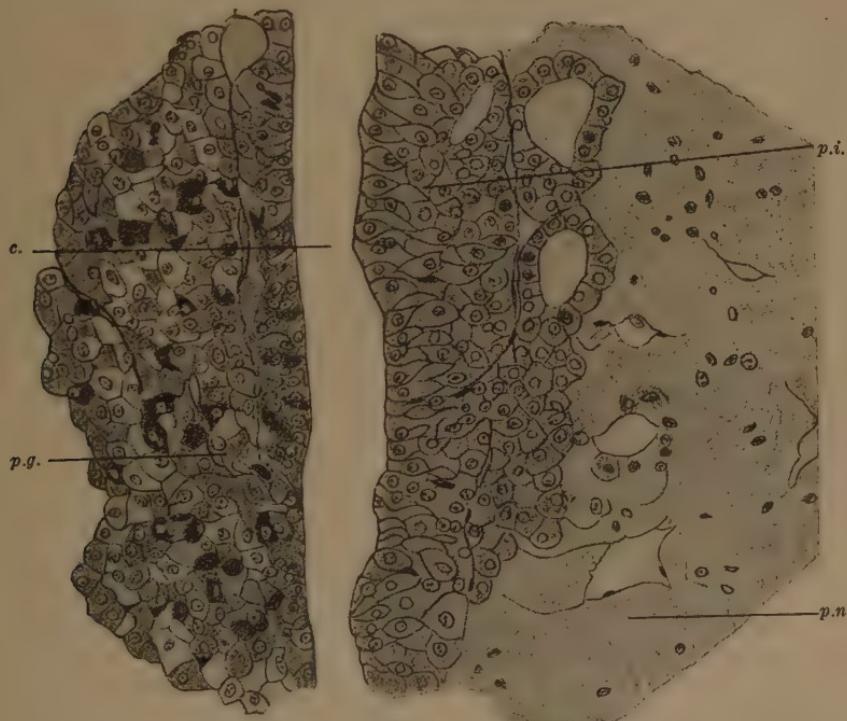


FIG. 287.—Section through a portion of the Pituitary Body of the Dog, showing the Glandular and Nervous Portions and the Pars Intermedia (from Swale Vincent).

*c.*, cleft in glandular portion (between glandular portion proper and the intermediate portion); *p.g.*, glandular portion; *p.i.*, intermediate portion; *p.n.*, nervous portion. In the glandular portion are seen three kinds of cells.

staining so that sections show pale and dark-stained cells mixed together. Like other internal secreting organs there is a plentiful blood supply.

The intermediate portion is developed from the anterior portion, but its function is related to the posterior portion. It consists of several layers of cells bordering the posterior margin of the cleft. The posterior portion is an outgrowth from the brain. In some animals it contains a cavity continuous with the third ventricle, but in man it is a solid structure, consisting of neuroglia containing masses of colloid material.

Marie (1886) was the first to describe a disease, acromegaly, associated with enlargement of the pituitary. Oliver and Schafer

showed that extracts of the pituitary caused rise of blood pressure with free flow of urine. Howell proved that when the anterior portion is separated from the posterior, the pressor substance is confined to the posterior part. As the separation takes place at the cleft the intermediate portion is associated with the posterior portion in causing the rise of blood pressure.



FIG. 288.—Twelve-months-old Hypophysectomized Dog (left) and Control from same Litter (Ashner).

The operation was performed at the age of eight weeks (from Schafer's *Endocrine Organs*, Longmans, Green & Co.)

anterior part. Partial removal of the anterior part interferes with growth causing decreased rate of metabolism, accumulation of fat, and diminution of sexual activity.

The evidence from experimental and clinical observations is that the anterior part is necessary for normal growth ; that over-activity of this part causes overgrowth of the skeleton, which if it occurs before the epiphyses are joined to the shaft produces gigantism, but if it occurs after this period it affects only the bones of the face, hands and feet, producing what is called acromegaly.

The posterior portion produces a substance which raises the blood pressure, causes increased contractions of the uterus and a flow of urine. It seems to act on unstriated muscle.



FIG. 289.—Hyperpituitarism with Giant Overgrowth.

Note the narrow chest, large joints and hypertrichosis. Compare the size of the hands with those of Dr. Crowe, whose height is 5 ft. 8 in. (from Cushing).

Hering has shown that the intermediate portion produces a substance which passes into the posterior portion to reach the ventricles of the brain.

**The Pancreas.** Removal of the pancreas causes interference with the metabolism of carbohydrates. The respiratory quotient falls, the amount of sugar in the blood increases and sugar appears in the urine. The defect seems to be due to the inability of the tissues to oxidize sugar with a compensatory increase in concentration of sugar in the blood. When the sugar concentration reaches a certain level sugar escapes into the urine. As these conditions mean a loss of valuable food material the body loses weight, although



FIG. 290.—To show the Facial Changes due to Acromegaly (Cushing). A, Patient before Onset of Disease (aged 18); B, at the Time of Onset (aged 26); C, on Admission after its full Development (aged 40).

the animal may eat an increased quantity of food. The defect is not due to absence of the digestive secretion of the pancreas, because ligature of the pancreatic duct does not produce the same defect. Further, if a portion of the pancreas be grafted at some other part of the body the symptoms do not occur.

Histologically the pancreas contains, in addition to its glandular portion, certain groups of cells with a large blood supply. These groups are known as *Islets of Langerhans*. The internal secretion of the pancreas is ascribed to these islets. If an extract of the islets is injected into an animal which has had its pancreas removed the symptoms due to removal are ameliorated. In order to obtain this extract the external secretion must not act upon active substance from the islets. This has been accomplished in four ways:

- (1) The pancreatic duct is ligatured, and after the glandular

cells have degenerated an extract of the remaining (islet) tissue is made.

(2) An extract is made from the foetal gland before the external secretion has become active.

(3) By extracting fresh gland with alcohol.

(4) By extraction in the presence of an acid. The active substance has been named insulin.

#### GLYCOSURIA (one of the symptoms of Diabetes).

Under certain conditions glucose is lost by passing into the urine.

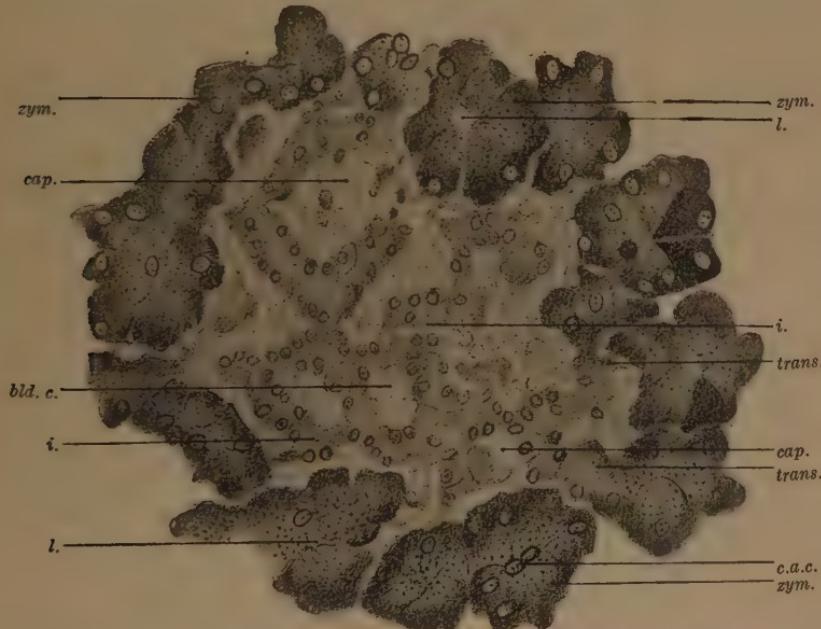


FIG. 291.—Islet of Langerhans, from the Splenic End of the Pancreas of a normal Dog, showing the Alveolar Form of the Islet Tissue (Vincent and Thompson).

The tissue of the islet is seen to consist of solid branching columns of cells, for the most part two deep, separated by wide capillary blood-vessels. *bld. c.*, red blood-corpuscles; *c.a.c.*, centro-acinar cells; *cap.*, blood-capillaries; *i.*, islet of Langerhans; *l.*, lumen; *trans. c.*, transitional cells; *zym.*, zymogenous tissue.

The various ways in which this result can be produced experimentally are :

- (1) By feeding a large amount of glucose (alimentary glycosuria).
- (2) By puncture of the floor of the fourth ventricle.
- (3) By removal of the pancreas.
- (4) By administration of drugs such as phlorizin.

(1) *Alimentary glycosuria.* This occurs when a sufficiently high concentration of sugar is produced in the blood. Excess of sugar in the blood can be produced by injection ; therefore injection of

glucose into the blood will produce the same effect. When the concentration of glucose exceeds 0·15 per cent., glucose can usually be found in the urine.

(2) *Puncture glycosuria* may be due to a vaso-motor disturbance. Stimulation of the nerves to the liver causes hyperglycæmia and glycosuria if the adrenals are intact : hence puncture glycosuria may be the result of nervous stimulation.

(3) *Removal of the pancreas*. This has been discussed above in relation to the function of the pancreas.

(4) *Phlorizin glycosuria*. Injection of this glucoside from the root-bark of apple, pear, cherry and plum trees causes glycosuria. In this form of glycosuria there is a defect in the permeability of the kidney, as the concentration of glucose in the blood is not greatly increased, but the oxidation of sugar in the tissues is also diminished.

Glycosuria usually results when the concentration of sugar in the blood rises above a certain level, which varies under different conditions. Thus adrenaline may cause hyperglycæmia and glycosuria. This result may be brought about by painting the adrenalin on the pancreas ; the effect, therefore, of adrenaline may be in part on the pancreatic hormone. As a result of glycosuria sugar is lost from the body, and it is for that reason that phlorizin glycosuria is used to investigate what substances can be turned into sugar in the body.

Whenever glucose is not being oxidized there is a failure to oxidize fats completely. Pancreatic glycosuria is generally accompanied by the excretion of  $\beta$ -hydroxybutyric and aceto-acetic acids. These "ketone bodies" remove a certain amount of base from the body.

Injection of insulin into a diabetic person causes a decrease in ketosis, a rise in respiratory quotient and a deposition of glycogen in the liver. These effects all depend on the restoration of the normal capacity of the organism to metabolize sugar.

On the other hand, the failure to oxidize sugar leads to its escape from the blood into the urine and a drain on the sugar reserves of the body, so that glycogen almost entirely disappears from the liver. Other substances, such as amino-acids, are converted into glucose with further loss to the body. Therefore the body loses weight in spite of a large intake of food.

We see that the metabolism is influenced by the hormones secreted by these various internal secreting organs. The secretion may be passed directly into the blood, of which there is a free supply to the various organs described, or it may pass into the lymph and reach the blood indirectly. It is probable that the activity of these organs may be correlated through the autonomic

system just as the muscular activities are correlated through the cerebro-spinal system. In this case we can look upon the autonomic system as correlating the metabolic activities and regulating the discharge of the internal secreting organs, where such discharge may be variable, e.g. in the case of the adrenals.

**The Thymus.** This is an organ which develops from the gill clefts. It is originally glandular, but the glandular substance becomes replaced by lymphoid corpuscles and all that remains of the gland is a series of circular cell masses representing the ducts (concentric corpuscles of Hassall). Thus, the thymus consists of

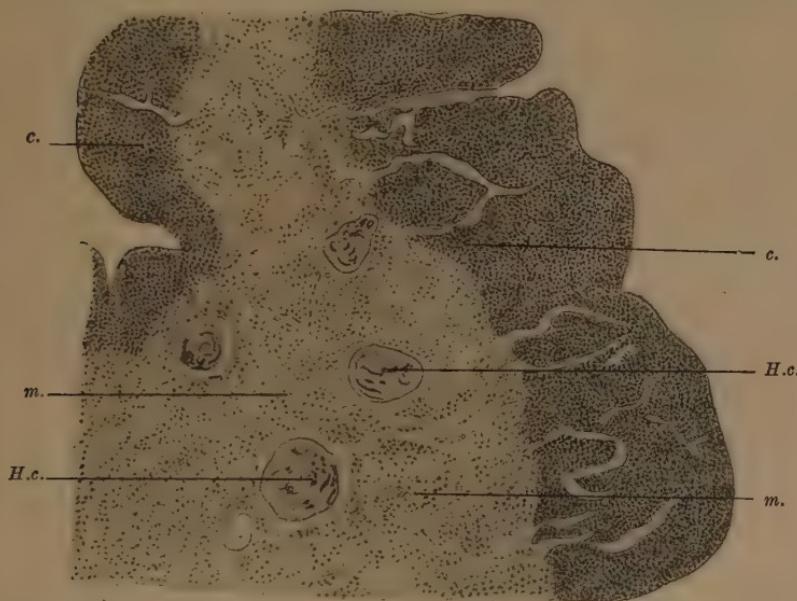


FIG. 292.—Portion of the Thymus Gland of a Monkey, as seen under a low power of the Microscope (from Swale Vincent).

*c.*, cortex; *H.c.*, Hassall's concentric corpuscles; *m.*, medulla.

irregular connective-tissue lobules containing lymphoid tissue, and in this lymphoid tissue are the concentric corpuscles of Hassall.

The function of the thymus is in some way related to the development of the sexual functions, as it generally atrophies about the age of puberty, but sometimes it persists. The persistence of the thymus and an increase in other forms of lymphoid tissue is frequently found in individuals who have died suddenly without sufficient obvious reason (*status lymphaticus*).

**The Testes and the Ovaries.** The secondary sexual characters are related to the sex glands, in the absence of which these characters do not develop. In both of these organs can be seen special

cells known as interstitial cells : they apparently have an origin independent of that of the reproductive cells and in appearance they resemble epithelial cells (epithelioid). In the testis these lie between the tubules (see Fig. 301) and in the ovary they are found in the connective tissue stroma. The evidence that the interstitial cells are responsible for the secondary sexual characters is that ligation of the vasa deferentia, with subsequent degeneration of the tubules of the testis does not cause loss of the secondary sexual characters whilst removal of the whole of the testes does cause their loss.

That interrelationships exist between the various internal secreting organs is probable, and it is often difficult for this reason to unravel the symptoms in clinical cases with supposed deficiency of internal secretions. Fig. 282B is suggestive of a relationship between the thyroid and the adrenals. The second tracing, B, shows a greater rise of pressure than the first one, A, whilst usually a second injection of adrenaline has less effect than the first one. Stimulation of the nerves to the thyroid apparently augments the activity of adrenalin.

NOTE.—For further information the student should consult Sir E. Sharpey-Schafer, *The Endocrine Organs*, Longmans, Green & Co.; Swale Vincent, *Internal Secretion and the Ductless Glands*, Edward Arnold & Co.

## CHAPTER XXXIX

### EXPERIMENTAL PSYCHOLOGY

As the human species is so highly educable it is difficult to determine how much of the nerve response in the human being is inherited.

If one moves a bright object before the eyes of a new-born child the eyes make irregular movements, but they cannot follow its movement, thus showing that the child sees the object, but that the muscular co-ordination is not yet developed. In two or three days the same child will move its eyes so as to follow a slowly moving object. Although such movements are still imperfect they show the training of the co-ordinating mechanism so that proprioceptive impulses from the eye muscles with the visual impulses together regulate the tension of the eye muscles. Such a process of training occurs whenever new co-ordinations are developed, e.g. learning to play golf or other games. In acquiring these accomplishments one must use conscious processes, i.e. one directs the processes by voluntary control, but when the movements have become perfected the attention is no longer directed towards them. Compare the anxiety displayed by a child learning to walk with the ease of an adult who can walk and perform other acts simultaneously. If the proprioceptive impulses are lost, as in locomotor ataxia, in which disease the posterior columns are destroyed, walking can be accomplished only by concentrated attention and the use of visual impressions. This need of conscious attention leads to rapid fatigue; we see therefore that by educating reflex responses the higher levels of the nervous system are saved for use where choice and selection are required.

In an earlier chapter we saw that stimuli which do not normally produce certain responses, may be linked by association with certain reflex actions, which are called conditional reflexes. A large amount of the development of an individual is due to the training of conditioned reflexes, so that certain associations of ideas link up various stimuli with definite activities.

That many such associations never reach the level of consciousness is illustrated in many ways. We move through a crowd, avoiding obstacles without noticing them. That such stimuli have been recorded somewhere is shown by hypnosis when many apparently unnoticed observations may be described. Again, we speak

to an individual engrossed in reading without receiving a reply, but we may find that the individual may come afterwards and answer our question.

In order that we can see or hear we must pay attention : the visual and auditory stimuli may, however, be received without our being conscious of them.

In Chapter XXXII we saw that inhibition is a most important process whereby the motor tracts may be correlated so that effector nerve impulses will not be interfered with by other patterns of discharge. That such inhibition occurs in sensory tracts may be shown in several ways. If we place in a stereoscope a card half red and half blue, and grey strips on non-corresponding parts of the visual fields, we may see a uniform purple background with an orange and a blue-green strip on it. These colours are the complementary of the backgrounds on which the grey strips are placed. The visual sensations should, however, correspond to the complementary colour plus the colour of the opposite field, which is stimulating the corresponding area of the other eye (see p. 413). When fusion fails and rivalry occurs there must be alternating inhibition of the impulses, so that at one time the sensation from one eye only is perceived.

Similarly, it seems probable that many associations and impulses from sensory organs do not reach the cortical interpreting mechanism. To indicate the large mass of impulses, memories and discharges which do not reach consciousness the term "*subconscious*" is used : it is sometimes difficult to transmit an impulse from the subconscious to the conscious.

In order that the cortical mechanism may be free to deal with fresh problems, once a mode of operation has been evolved the routine performance of that process does not always affect consciousness. Unpleasant associations disturb conscious processes, hence there seems a tendency to inhibit their too frequent intrusion. When an unpleasant impulse is prevented from reaching consciousness all associated phenomena may be also barred, so that loss of memory of an unpleasant occurrence may sometimes involve loss of memory of many events associated with it either in time or space.

Sometimes a thought or afferent impulse which has not been brought into relation to other factors in the mental furniture is relegated to lower mental levels. As the subconscious machinery cannot deal with these unassimilated nerve impulses there is a continual conflict between the unassimilated and assimilated ideas : these should be sorted by consciousness and the whole assimilated. Sometimes, however, owing to inhibitory action, the complex cannot be sent back for resorting. The inhibitory process is given the picturesque name of "The Censor," and the process of inhibiting

the complex is called *Repression*. The interference with the normal subconscious processes due to unassimilated material leads to attempts to reconsider the subject, but inhibition prevents this; thus there is a continual wear-and-tear which may lead to what is termed a *psycho-neurosis* or a disorder of the normal psychical processes. The offending material may be presented to consciousness in symbolic form, especially in the form of dreams.

Our impulses and emotions can be divided into two sets, namely those which are purely selfish and those which are more or less altruistic; the proper apportionment of activity between these two sets is the province of *Ethics*.

If we attempt to reduce the altruistic tendencies to a common basis we find that they are all directed to the continuation and improvement of the human species. For this purpose we must make our selfish impulses sometimes subservient to the altruistic ones. For instance, self-preservation is a legitimate impulse even from the point of view of the continuation of the species, but sometimes it is necessary to disregard self-preservation for the attainment of an ideal which makes for better conditions for the race as a whole. For the purpose of allowing the altruistic impulses to dominate the organism the selfish impulses must be inhibited just as one reflex is inhibited to allow another more important one to take place.

As it is not always easy to know which emotion ought to be allowed to dominate the organism we are often guided by rules or conventions which are useful, as they express a certain amount of accumulated experience, but they ought not to be allowed to dominate one's activities. The great advantage of correct training is that it develops associations so that one often does the right action without having time to think whether it is or is not the best to do in the circumstances.

In the event of bad training the subconscious response is often antisocial and such a condition is difficult to overcome because early associations are believed to be more firmly established than those acquired later in life. That new associations may be developed is shown by what are called "conversions," when, under the influence of a religious emotion, an individual determines to lead what he believes is a different and better life. If this resolve persists a conscious re-education may develop new associations, so that the individual's actions are now social instead of anti-social: rules of conduct may help in the development of such re-education. That a similar re-education may occur by a gradual development is not unlikely, but one must start the process by creating some controlling impulse, so that the individual works out for himself what he believes to be the correct associations.

It is because of the influence of early associations on subconscious

responses that the correct education of children is so important. If education has been on lines that are directed to the amelioration of human conditions, so many decisions in after-life are rendered easier. Thus an individual who has been brought up to look upon freedom of thought and action as essential conditions of improvement will be willing to risk his life for conditions of freedom. He who has not developed such associations will save his skin by being unwilling to fight and then, by calling himself a "conscientious objector," refuse to acknowledge, perhaps even to himself, that his instinct for self-preservation has inhibited his herd instincts.

This brief discussion is intended to emphasize the fact that inhibition is as important a factor in the mental life of an individual as it is for the physical reflex mechanisms.

**Sleep.** The activity of the brain is periodically interrupted by sleep. This is a condition of unconsciousness which may vary in degree. It has been studied experimentally by applying stimuli such as sounding a bell and finding the intensity of the stimulus necessary to awaken the sleeper. It has been found that sleep is soundest soon after its commencement, and that the depth of sleep decreases until the natural awakening occurs. Control of the body is decreased during sleep. This can be seen, for instance, by the relaxation of tone in skeletal muscles.

The condition of the conducting paths during sleep is unknown. Two conflicting views are held, namely that there is an increased resistance at the synapses or that there is a decreased resistance. The former view is that impulses cannot pass through the nervous system because of the resistance, whilst the latter view is that the impulse, being able to pass in any direction, is dissipated and becomes ineffective.

Anæsthesia and narcosis are conditions similar to sleep produced by the action of drugs : the interruption of conduction may be caused by interfering with any part of the conducting path ; for example, spinal anæsthesia is produced by the local action of a drug, e.g. stovaine, on the dorsal roots of the spinal cord. Local anæsthesia is an interruption of the conducting path by injection of the anæsthetizing substance into a nerve sheath, or close to the sensory nerve endings.

**Hypnosis** is a condition brought about in various ways, whereby stimuli fail to affect consciousness ; for instance, pain is not felt when a needle pierces the skin. The individual may say or do things without being conscious of them afterwards. It seems as if the conscious part were separated from the rest of the body and events may be described which were forgotten by the conscious individual. Further, the hypnotized person may be instructed to do something at a given time and after recovery from the hypnotic

condition he will carry out the instructions without any conscious knowledge of the suggestion made during hypnosis. Pawlow believes that hypnosis and sleep are both the result of inhibition.

**Psycho-analysis.** Earlier in this chapter it has been stated that certain unpleasant associations may be repressed by inhibition, i.e. kept from interfering with consciousness. The evidence for this statement is based on attempts to analyse the influences that underlie our conscious mental activities. It is not possible to prove that such inhibition interferes with mental processes, but the results of treatment based on that assumption suggest that such interference does occur.

THE METHODS used to investigate the non-conscious processes are :—(1) Interpretation of Dreams ; (2) Hypnosis ; (3) Free association ; (4) Word association tests.

*Dreams.* It is claimed that dreams may incorporate recent events and actual bodily stimuli, but that they frequently present unassimilated material from the subconsciousness which has been sufficiently disguised to pass "the censor." Whether this is true or not is difficult to prove, but many cases have been published in which the interpretation of the dream has been acknowledged by the individual as representing some unpleasant incident which he had apparently forgotten, the forgetting being the inhibition which Freud has designated as the censor.

*Hypnosis.* By hypnosis it is possible to obtain accounts of events which have been apparently forgotten. Thus amnesia due to war conditions seems to be a repression of unpleasant conditions ; such repression frequently blots out all the associated conditions. Memories recalled by hypnosis have been confirmed in some cases by independent evidence : thus there seems to be a large number of memories stored in the mind which can be brought to consciousness by special means, but it does not necessarily follow that every event in one's life is stored away somewhere and may be recalled by appropriate means.

*Free association* is sometimes employed in the interpretation of dreams. This consists in allowing one's consciousness to start from some event and wander on from thought to thought without attempting to suppress anything. In this way it may be possible to find links between certain associations which relate to some previous event in the individual's life.

*Word Association* is related to the measurement of reaction times. Just as it is possible to measure the time interval between the application of a stimulus and the response of a muscle, so it is possible to measure the time interval between a sound, a sight or a touch and a muscular response. The apparatus which is used consists of an electrical circuit including two keys and a magnet.

One key,  $K_1$ , on being opened produces a sound, a visual impulse (movement or light) or a touch and at the same time moves a signal.

The observer actuates this key, whilst the subject is told to close the second key,  $K_2$ , as soon as he perceives the stimulus. Closing the second key short-circuits the magnet; hence the interval between the two movements of the signal gives the reaction time. The signal may record on a moving drum, or be linked with a clock, so that the hand moves only during the period whilst both keys are open.

FIG. 293.—Diagram of the Apparatus for the Determination of Reaction Time (W. G. Smith).

The electro-magnetic tuning-fork  $T$  with 100 vibrations per second is connected with two Daniell cells and the signal  $C$ . By means of either of the keys  $K_1$  and  $K_2$  the signal can be short-circuited.  $K_1$  is closed and  $K_2$  open. The experimenter opens  $K_1$ , which also serves as the stimulus, and the subject is to close  $K_2$  as soon as the stimulus is noticed. As the signal records the vibrations of the tuning-fork only whilst both keys are open, the number of vibrations recorded gives the reaction time in  $1/100$  secs.

open. The clock records in hundredths of a second.

The dilemma or choice of reaction shows the extra time required for conscious decisions. Thus, if several lights of different colours

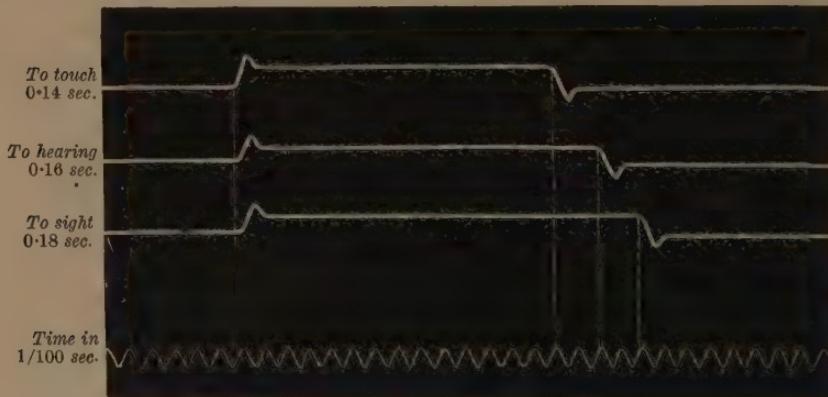


FIG. 294.—Reaction Times to Touch, Hearing and Sight (Waller). Recorded by air transmission and tambour, not by the electrical method shown in Fig. 294.

are employed and the individual is to respond to one only, we find that the reaction time is considerably longer. The word association test consists of reading out a series of words and asking the subject to respond with whatever word he associates with the one read out.

A few examples of such associated words are "black," to which the response might be "white"; "smooth," "rough"; "hard," "soft," etc.

The usual time for a response is about two seconds. If an unusual association word is given it may be of significance, but the time of response is still more significant. A delay in the response, which may be so great that no response occurs, suggests that the natural response of the individual has been inhibited, thus giving evidence of a repression associated with the stimulus word.

*The Psycho-Galvanic Reflex.* A means of testing emotion is the psycho-galvanic reflex. This consists in measuring the impedance to the constant current by a part of the subject's body, usually his hand. The apparatus consists of a Wheatstone Bridge and galvanometer. When the balance has been obtained it is found that if the subject displays emotion the impedance is decreased and the galvanometer shows the lack of balance of the circuit. Emotion may be produced by the prick of a pin, the threat of a prick or a burn, by a sudden noise or by other means. If a word stimulus be used and an emotional association occurs the galvanometer will show that such an association has occurred.

By these various means it is possible to obtain some information about the emotional constitution of the individual, often information that could not have been furnished by the subject because the facts discovered had been lost to conscious recall.

**PSYCHO-THERAPEUTICS.** The application of these ideas to the treatment of disease has given very good results in some cases.

Unassimilated material forced out of consciousness may lead to disturbed reactions on the subconsciousness. Loss of memory associated with events in warfare is one example of such disturbance.

Again, hysterical symptoms, such as paralysis or loss of sensation, may be the result of a conflict between duty and self-interest. By becoming paralysed one may escape from a dangerous employment without the conscious feeling of neglecting one's duty. Dis-

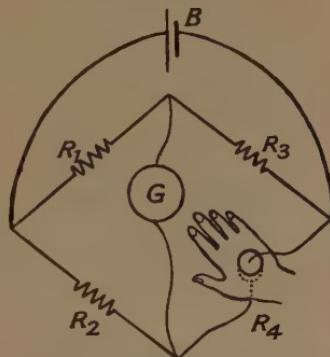


FIG. 295.—Diagram of Wheatstone's Bridge Method of Measuring Electrical Resistance.

$B$  = battery,  $G$  = galvanometer,  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are the resistances of which the values of  $R_1$ ,  $R_2$  and  $R_3$  are known. When no current is flowing through the galvanometer,  $R_3 : R_1$  as  $R_4 : R_2$ . The change in resistance of the hand during the psychogalvanic reflex upsets the balance so that a current flows through the galvanometer which causes a deflection of the recording mechanism. For the measurement of alternating currents the battery is replaced by an alternating source of current, e.g. an induction coil, and the galvanometer is replaced by a telephone.

sociation of this sort may be so marked that two different individualities may seem to alternate in the single body. The various impulses of a normal individual are integrated, but when this integrating power is lost dissociation of the personality occurs, and the loss of control over muscles or loss of appreciation of sensation is a minor degree of such dissociation.

The treatment of such cases is to recall the lost memory by psycho-analysis, or to find out what special lack of co-ordination of the individual with his surroundings exists. Sometimes the mere recall of the memory accompanied by the emotion which has been suppressed is a large factor in restoring the individual to health. This recall of emotion is termed the *abreaction*.

According to Freud the usual lack of co-ordination between the individual and his surroundings is repression of some sexual factor. That the repression of other impulses, such as self-preservation in war-time, plays a part has been indicated above.

Physiologically the normal response to a stimulus is some reflex : the normal sequence to an emotion is action. When the normal outlet of an emotion is inhibited there may be danger of some form of repression which may affect the health of the individual. Where normal outlet is undesirable it is found that the emotion may be diverted to some other purpose. Physical outlet for emotion in some cases may be found in games, gardening, etc. ; a common form of outlet for emotion is in philanthropic undertakings. This process of finding an outlet for emotion so that it is not repressed but directed to useful purposes is known as *sublimation*.

Many of the effects produced by repressions are due to activities of the autonomic nervous system, and the curing of psycho-neuroses will produce improvement in bodily activities through that system. Emotion probably sets free adrenalin, therefore muscular activity is required to "work off" its effects.

In this final chapter on the controlling mechanisms some attempt has been made to indicate the application of the physiological mechanisms to mental processes. Experimental psychology started as a branch of physiology by studying the special senses and reaction times. From mere sensation and reflex response it went on to study memory and now it represents a seething mass of accumulating data from which we have attempted to select such material as seemed suitable from the point of view adopted in this book towards controlling mechanisms.

NOTE.—For further information on the subject discussed in Part III the student should consult C. S. Sherrington, *Integrative Action of the Nervous System* (Yale University Press); S. W. Ranson, *Anatomy of the Nervous System* (W. B. Saunders Co.)

## PART IV

### MAINTENANCE OF THE INDIVIDUAL AND REPRODUCTION OF THE SPECIES

In Parts I and II the physical and chemical reactions of living organisms have been described, and in Part III the control exercised on the individual processes has been outlined. It remains now to consider the conditions for the maintenance and reproduction of the individual.

Maintenance of an individual may be considered from several aspects. Firstly, there are those general conditions associated with nutrition and the intake of food materials ; and, secondly, there are those factors which depend upon the environment, that is the effect of climate and the reaction of the body to parasitic organisms.

For the continuation of the species we find that it is necessary to study how one generation passes on its characters to the next, the process whereby new individuals are initiated, and finally the growth of the new individual.

## CHAPTER XL

### MAINTENANCE OF THE INDIVIDUAL: NUTRITION

In order that the individual may be maintained in health sufficient material must be taken into the body to make up for the daily loss, a problem which involves the consideration of metabolism. The total energy expenditure is that amount necessary to maintain the minimal vital activities of the tissues (body cells, heart activity and respiration) to compensate for the loss of heat and to allow for the increased expenditure due to bodily movements. It is somewhat difficult to separate these three conditions.

**Basal Metabolism.** The maintenance value is sometimes considered to be what is known as the basal metabolism. This is the energy expenditure as calculated from the oxygen intake and carbon dioxide output when the individual is lying quietly, in warm surroundings, and fifteen hours at least after the preceding meal. This last condition is necessary so that the alimentary canal will have finished the processes of digestion, thus being in a quiet condition. Though of course such conditions are more or less arbitrary as slight movement of skeletal or other muscles may occur, measurements of basal metabolism are nevertheless used for clinical purposes.

The usual values obtained under such conditions are about one large calorie per kilo per hour, or forty large calories per square metre per hour. For a man of 70 kilos and a surface of 1.75 sq. metres, the daily output would be  $70 \times 24 = 1,680$  calories =  $40 \times 1.75 \times 24$ .

**Effect of External Temperature.** As the human subject maintains a temperature more or less independent of his surroundings a fall of external temperature will cause an increased loss of heat. Although, as shown previously (p. 489), compensation may occur by allowing the skin to cool slightly, there must still be an increased heat production if the temperature of the body is to be maintained. Experiments have been made with the results shown in Table LIX, page 493.

How this increased heat production is brought about is not quite certain. Cold weather leads to increased muscular activity, but

in the experiments quoted the individuals were resting under both conditions. Shivering is a means of heat production by muscular activity, but even in the absence of shivering increased heat production may occur. It has been suggested that increased muscle tone causes increased heat production, but the condition of decerebrate rigidity, which in some respects resembles tone, does not lead to increased oxidation. The maintenance of rigidity may not require extra oxidation, but the production of rigidity would require an expenditure of energy. Therefore if variations of tension occur in different parts of the same muscle extra heat production would occur without noticeable movement, a condition which might culminate in the visible movement of shivering. The glands of various sorts, e.g. the liver, are another possible source of extra heat production.

This effect of temperature on metabolism is reflected in the well-known fact that more food is required in cold than in warm weather. The stimulating effect of cold is useful in "toning up" the organism as shown by the effect of open air treatment for malnutrition.

**Effect of External Work.** External work increases the oxidation processes in muscles as well as causing an increased expenditure of energy by the circulatory and respiratory processes. The amount of energy expended in external movement depends not only on the amount of work done, but also on the nature of the work.

Thus we see that the total energy expenditure of the body requires a consideration of a number of factors which are not, however, purely additive. Thus increased muscular work in cold weather may supply sufficient heat for the extra loss due to the lower temperature, and the energy expenditure for that amount of work may be the same or very slightly increased over that for the same work at a higher temperature.

The following figures are given as average requirements of normal adults under different conditions, and the food should contain sufficient energy value for the appropriate condition.

TABLE LX  
ENERGY OUTPUT

|                                |       |                |
|--------------------------------|-------|----------------|
| Man at rest . . . . .          | 1,680 | large calories |
| Sedentary occupation . . . . . | 2,500 | "              |
| Active outdoor life . . . . .  | 3,500 | "              |
| Severe manual labour . . . . . | 5,000 | " or more.     |

In considering the above figures one must remember that the net values are less than the gross values, as furnished in the diet, by an amount which will vary with the ease of digestion of the food eaten.

**Nitrogenous Equilibrium.** As protein is not stored to any appreciable extent, an increased intake is followed by an increased output. Nitrogenous equilibrium can therefore be maintained at a series of levels. If no nitrogenous food is taken, but sufficient energy value is supplied in the form of carbohydrates and fat, the excretion of nitrogen will reach a minimum level. Addition of the equivalent amount of protein in the diet will cause an increased excretion of nitrogenous substances, and therefore a larger amount must be given to maintain equilibrium. By increasing the amount of protein in the diet a condition of equilibrium can be produced when the protein intake corresponds to between three to five times that of the minimum nitrogenous excretion. Above this value equilibrium will exist, no matter how much protein is administered, as the excretion keeps pace with the intake. The increased oxidation which accompanies the taking of protein food is known as the *specific dynamic effect of protein*.

**Protein Requirement.** The protein requirement is based on the need for certain amino-acids. Unfortunately we cannot give a list of the essential amino-acids and the amounts of each required. Amino-acids, which can be formed from other substances, need not be present as such in the diet, so that we can say that the amino-acids required by the body are those which are essential to life and are not formed in the body itself. The amounts of these required will depend upon the quantities destroyed each day. The amount of protein, therefore, as judged by the total nitrogen will vary with the amount and variety of the amino-acids present in the protein. The disease pellagra, for instance, may be the result not of lack of protein as such, but of lack of certain amino-acids, e.g. tryptophane. It must be remembered that it is not the amount eaten, but the amount absorbed, which is the essential factor.

Rats fed on zein, the chief protein of maize, lose weight and ultimately die. Zein is deficient in tryptophane and lysine. The addition of tryptophane prevents the loss of weight, but the addition of lysine does not. On the other hand in order that the animals can grow, lysine and tryptophane must both be added (Hopkins and Osborne and Mendel.) It has been shown that growing animals require some amino-acids which do not seem necessary in adults of the same species.

A diet restricted to one form of protein is dangerous unless one is certain that that protein contains all the necessary amino-acids. Caseinogen, for instance, lacks glycine, yet it can be used as the sole source of protein in the diet, thus indicating that glycine can be synthesized. The amino-acids which are believed to be necessary and not synthesized in the body are lysine, phenylalanine, tyrosine, tryptophane, histidine, and cystine.

In the absence of accurate information as to the exact amino-acids required per day, the figures of K. Thomas (Table LXI) are useful in estimating the biological value of protein. He found the amounts of different proteins required for equal "tissue-repairing" values.

TABLE LXI  
"BIOLOGICAL VALUES" OF PROTEINS (THOMAS)  
(Cow's milk being taken as the standard of comparison)

| <i>Source of Protein.</i> | <i>Comparative<br/>"Tissue-repairing"<br/>Value.</i> | <i>Comparative<br/>Weight<br/>Required.</i> |
|---------------------------|--|---|
| Beef . . . . .            | 104  | 97  |
| Cow's Milk . . . . .      | 100  | 100   |
| Fish . . . . .            | 95   | 105   |
| Rice . . . . .            | 88   | 114   |
| Potato . . . . .          | 79   | 127   |
| Caseinogen . . . . .      | 70   | 143   |
| Peas . . . . .            | 56   | 180   |
| Wheat Flour . . . . .     | 40   | 250   |
| Maize . . . . .           | 30   | 333   |

These values are not definitely established. For instance it is doubtful whether maize can serve indefinitely as the only source of protein over a long period of time.

Bearing these considerations in mind we see that the minimum amount of protein required is a variable figure depending on the kind of protein used. The figures given by the writers of twenty years ago are too high, as Chittenden showed by a series of experiments in which he obtained maintenance with about 60 gm. per day. Lindemann has obtained equilibrium with even lower figures down to 40 gm. per day.

It is probable that an allowance of 80 gm. of protein from a good mixed diet is sufficient for most purposes. Of course if the energy value from other sources is defective, so that some of the protein must be utilized merely as a source of energy, more protein would be required.

**Carbohydrate and Fat.** These two substances are exchangeable to a certain extent and we speak of their isodynamic equivalents in the sense that one gram of fat gives the same energy value (9.3) as 2.27 gm. of carbohydrate ( $2.27 \times 4.1$ ). A balanced mixture of the two is preferable to an exclusive diet of either. Excess of fat is more difficult to digest, and the metabolism of fat requires a simultaneous oxidation of carbohydrate as lack of carbohydrate leads to the excretion of  $\beta$ -hydroxybutyric acid, aceto-acetic acid, and acetone. On the other hand excessive cold or excessive work may require relatively more fat because of its more concentrated energy value: the large amount of carbohydrate required might be more than the alimentary canal could deal with. Starling

suggests that at least twenty per cent. of the total energy requirement should be in the form of fat. Apart from this restriction the relative amounts of carbohydrate and fat in the diet are a matter of taste.

**Salt Requirement.** On most mixed diets the amount of salts is sufficient, but in special conditions or with over-refined foods there may be a deficiency or a misproportion of salts. Many inorganic substances are required for special purposes, and these must be present in adequate amounts. Calcium, phosphorus, iron, etc., are all required in addition to sodium chloride.

**Accessory Food Constituents (Vitamins).** In addition to the above well-known constituents food must contain certain unknown substances the presence of which can be shown only by the effects of their absence on the health of animals. The less the amount of a food material, which suffices to cure or prevent the symptoms due to a vitamin deficiency, the more concentrated is the vitamin in that substance.

At least three distinct substances are recognized, namely, fat-soluble A, water-soluble B, and water-soluble C, and they vary in their stability to chemical and physical agencies. Fat-soluble A is rapidly destroyed by oxidation; thus exposure to air, especially when the material is heated, causes a rapid falling off in its activity. Water-soluble B is not destroyed by heating even in the presence of air. Water-soluble C is very easily destroyed by heating or even by drying, but it is possible to prepare concentrated solution of it from lemon juice. There is a growing amount of evidence that these vitamins are not single substances; thus experiments indicate that there may be two separate substances included as fat-soluble A. It is also claimed that water-soluble B contains some substance which prevents beri-beri, and another which promotes the growth of yeast in synthetic media.

**Fat-Soluble A.** This is associated with certain fats, and when young animals are fed on a purified diet from which all fat-soluble A has been excluded they fail to grow. Both young and adult animals frequently develop corneal ulcers (keratomalacia) when they are living on a diet deficient in fat-soluble A. In addition to its action in preventing keratomalacia, it is said to have some effect in preventing rickets, and these two effects may be due to different substances. Absence of fat-soluble A from the diet of growing puppies causes rickets, but other factors are of importance; thus it has been found that exposure to sunlight and fresh air enables animals to thrive on smaller quantities of fat-soluble A than when they are indoors. Ultra-violet radiation also has some effect on the metabolism in relation to the amount of fat-soluble A necessary for health.

Most animal fats except lard contain fat-soluble A, but vegetable fats are relatively deficient in it. Butter sometimes contains a fair amount of it, but as the supply of fat-soluble A depends upon the diet, the amount in the milk and butter will vary with the nature of the animal's diet. Cod-liver oil is about 250 times as potent as average butter in preventing the symptoms associated with lack of fat-soluble A. Green parts of plants contain fat-soluble A, and it is probable that they are the source from which all animals obtain their supply of it. The test animals are usually rats.

*Water Soluble B* is associated with the pericarp and embryo of cereals, with yeast and with the green parts of plants. Its absence from the diet causes paralysis, which is rapidly cured by small doses of extracts from the parts of plants containing it. It is claimed that absence of this substance is the cause of beri-beri, which is generally the result of eating polished rice, i.e. rice deprived of its pericarp and embryo. The test animals are usually birds.

*Water-soluble C* is present in fresh meat and vegetables. Its absence from the diet leads to weakness and subcutaneous haemorrhages, thus corresponding to the disease, scurvy. The test animals are usually guinea-pigs.

**Starvation.** When an individual is starved the easily available stores are used up, after which the body tissue is drawn upon. The most immediately available store is glycogen, and this is rapidly reduced in amount during the first day or two, after which the fats are mobilized. As the amount of available carbohydrate is decreased there is a corresponding increase in the utilization of fat. During the early stages of starvation the loss from the body is reduced to the lowest possible level which suffices to maintain the body temperature, and to furnish energy for the body movements.

As there are no nitrogenous substances coming into the body there is a rapid decline in the excretion of nitrogen to a low level. The nitrogen excretion remains at a low level until the stores of carbohydrate and fat are nearly exhausted, when the proteins of the cells are required for the supply of energy, which causes an increase in the excretion of nitrogen in the urine, and this rise is a danger-signal showing that most of the food reserves are exhausted. During the whole period of starvation there is a drain upon the tissue proteins as shown by the daily excretion of urea. This minimum loss, however, falls on the less essential tissues, as shown by the relative amounts of tissue lost during a period of starvation. The increased use of fat during starvation is shown by a fall in the respiratory quotient. The amount of fat carried to the liver is so great that after a day or two of starvation analysis of the liver shows an increase in fat, and the fat may be visible as fat globules in the liver cells (Mottram).

Thus during starvation there is a fall in the excretion of nitrogen, a using up of carbohydrate and of fat. The amount of protein destroyed is a minimum until the reserves of carbohydrate and of fat are nearly exhausted, when a terminal increase in nitrogenous metabolism occurs.

Increased metabolism of fat with deficiency of carbohydrate leads to ketosis during starvation. It is well to point out that the respiratory quotient is due to the sum of the oxidations of carbohydrate, fat and protein. The changes during starvation show merely

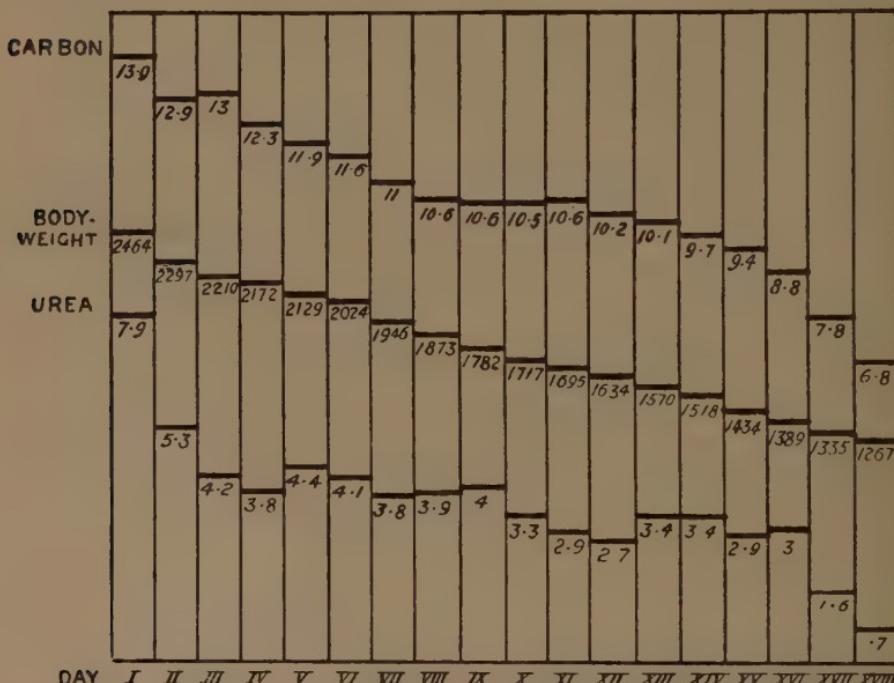


FIG. 296.—Graphic Representation of the Declining Weight and the Daily Excretion of Carbon and Urea by a Starving Cat (Data by Bidder and Smith).

(From Waller's *Human Physiology*, Longmans, Green & Co.)

a relative alteration in the proportions of the substances oxidized and carbohydrate is still present even in the later stages. During preparation for hibernation a high respiratory quotient up to 1.3 indicates a conversion of carbohydrate into fat, while a low respiratory quotient during hibernation (0.3) suggests that fat is being converted into something containing more oxygen, and is not being completely oxidized.

**Dietetics.** In arranging a diet all the factors described above must be included. One may analyse the food or one may consult tables showing the composition of various foods. The former procedure is more reliable as different samples of the same food

may vary in composition, but the latter method is more often followed. The food tables usually indicate the amount of waste material (such as skin, etc.) in the food as purchased.

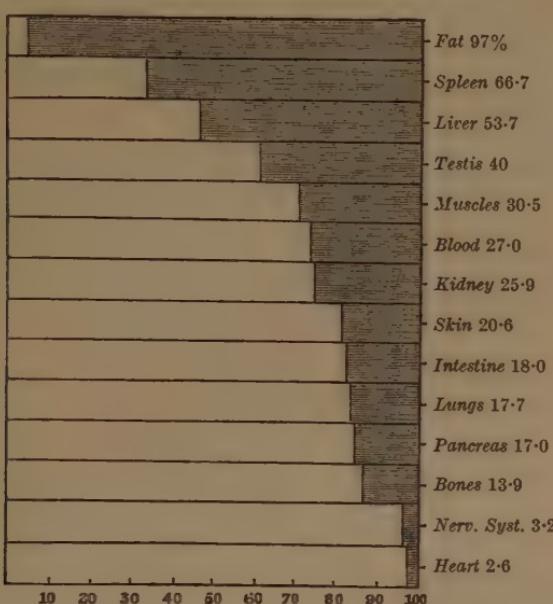


FIG. 297.—Graphic Representation of the Percentage of Different Tissues Lost during Starvation.

The shaded areas represent loss, the unshaded areas residue at death (according to Voit's analyses) (from Waller's *Human Physiology*, Longmans, Green & Co.).

TABLE LXII  
DIET FOR A YOUNG MAN DOING LIGHT WORK

For the composition of the Food Substances, Table XI, page 133, must be consulted.

| Food Substance.              | Amount<br>in gm. | Protein<br>in gm.<br>Gross. | Biological<br>Value. | Fat<br>in gm.             | Carbo-<br>hydrate<br>in gm. | Energy<br>in C. |
|------------------------------|------------------|-----------------------------|----------------------|---------------------------|-----------------------------|-----------------|
| Bread . . . .                | 500              | 36.00                       | 14.4                 | 1.00                      | 240.5                       | 1,143.0         |
| Beef . . . .                 | 100              | 18.84                       | 19.6                 | 18.39                     | 0.0                         | 248.3           |
| Butter . . . .               | 50               | 0.20                        | 0.2                  | 40.80                     | 0.0                         | 379.4           |
| Potatoes . . . .             | 500              | 10.50                       | 8.3                  | 0.25                      | 95.0                        | 435.0           |
| Cheese . . . .               | 25               | 6.30                        | 4.4                  | 8.40                      | 0.0                         | 106.9           |
| Total . . . .                |                  | 71.84                       | 46.9                 | 68.84                     | 335.5                       | 2,312.6         |
| Energy value of constituents |                  | 294.5                       | +                    | 640.2 + 1,375.5 = 2,310.2 |                             |                 |

If to such a diet as that given in Table LXII, a certain amount of fresh fruit and green vegetables is added it will form a moderately complete diet. Small amounts of additional substances produce variety and variety is valuable in facilitating digestion.

Instead of working out the individual energy values for each constituent we can determine the total protein, carbohydrate and

fat of the diet and multiply these by the corresponding energy values, from which the total energy value is obtained. As shown in the last line of Table LXII, the energy value so obtained is practically the same as the sum of the energy values of the individual food substances. The energy value for protein and carbohydrate being the same, the amounts of these substances may be added together before multiplying by the energy value.

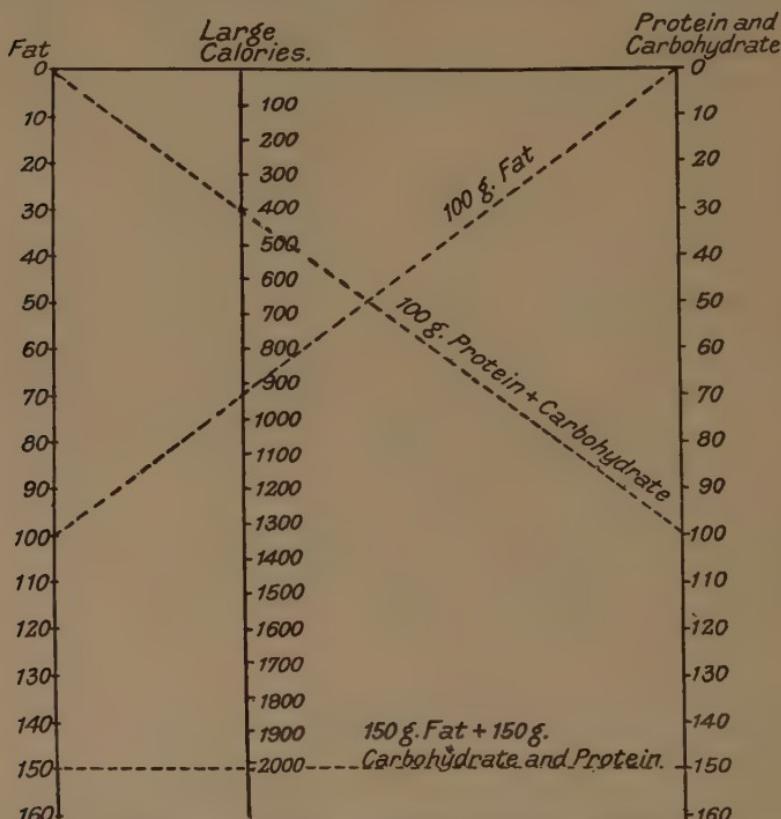


FIG. 298.—Nomogram showing Uniplanar Relation between three or more Variables.

The interrupted lines show the calorie value of certain weights of food substances (W. A. M. Smart).

A rapid method for calculating the energy value of a diet is to use a nomogram. This is a series of lines so arranged that a single straight line cutting them will show several corresponding values. In the example shown three dotted lines show respectively the energy value of diets containing 100 gm. of protein and carbohydrate, 100 gm. of fat, and 150 gm. of protein and carbohydrate, as well as 150 gm. of fat.

## CHAPTER XLI

### MAINTENANCE OF THE INDIVIDUAL: REACTION TO THE ENVIRONMENT

The effect of environment on an individual is due to the action of the climate, and to reactions with parasitic organisms.

#### *CLIMATE*

Variations of climate are due to the distance of a country from the equator, its proximity to large bodies of water, the direction of the prevailing winds, the slope of the land and its height above sea level. From the physiological point of view we can classify the effects of climate under the headings of temperature, moisture in the air, movement of the air and barometric pressure. The first three of these are related to heat loss, and they will be considered together whilst the variations of barometric pressure will be described by themselves.

#### VARIATIONS IN TEMPERATURE, MOISTURE AND MOVEMENT OF THE AIR

**Cold Climates.** It will be most convenient to take a temperate climate as a standard and indicate the effect of deviations from that standard.

A cold climate is one with a low temperature. This also implies a small amount of water vapour in the air as shown by Table LVII (p. 489).

The heat loss of the body depends on the evaporation from the surface, and the loss by radiation and conduction as described previously (p. 490). A low external temperature means a greater heat loss, and therefore a greater heat production is required if the body temperature is to remain the same. The heat loss can be diminished by the processes of regulation, but the effect of a low temperature cannot be entirely obliterated by the regulating processes. In very cold climates the heat loss can be reduced by surrounding the body by a layer of warm air. The ease with which this layer may be kept warm depends upon the gradient of tempera-

ture between the layer next to the body and the external air. In order to decrease the temperature gradient the thickness of the clothing can be increased. Next to a vacuum, the best non-conductor is a gas, and therefore air spaces are important heat insulators. For this purpose loosely-woven bulky clothing is the best. In order to prevent the warm air in the clothing from being removed by air currents the outside of the layers of clothing should consist of some wind-proof material, and this material should overlap well at all joins so as to diminish any draughts.

It is difficult to understand why damp cold air seems colder than dry cold air. It is not due to the heat capacity of moist air being greater than that of dry air. Osborne has suggested that the moisture causes swelling of the surface cells of the epidermis. The air spaces in the skin are decreased in size by the swelling, therefore the damp air causes increased conduction to the surface of the skin with cooling of the dryer layers where the temperature organs are situated.

**Hot Climates.** In hot climates the rate of heat loss by radiation and conduction is decreased ; in fact when the external temperature is above that of the body gain of heat must occur by conduction and by radiation. As the external temperature rises the heat loss must be dependent more and more upon evaporation. The actual volume of water vapour which can be held in a given volume of air is limited (see Table LVII). One sees, therefore, the importance of air currents to remove the moist air. A warm moist atmosphere is more enervating than a warm dry atmosphere, largely because less evaporation can take place.

Clothing for hot climates should contain as large air vents as possible. Open texture is not so important as air holes.

**Failure of Temperature Regulation.** Excessive loss of heat will lead to a fall of body temperature. When too great heat loss occurs the activities of the body will slow down, and ultimately death will occur. The individual becomes drowsy and ultimately falls asleep, never to wake up. Excessive heat loss may be due to extreme cold or to failure of heat regulation. Anæsthetics, for instance, interfere with the heat-regulating activities, hence unconscious individuals must be surrounded by warm air in order to prevent excessive heat loss. Hot drinks and hot food help to maintain the body temperature.

When heat loss does not keep pace with heat production the body temperature rises. In hot climates failure of the secretion of sweat leads to hyperpyrexia and death. Under such conditions the only remedy is to imitate sweat evaporation by wrapping the individual in a wet sheet and causing air currents by an electric fan or a punkah.

*Heat stroke* consists of two varieties, one in which the person is in a cold clammy condition, the after-effect of an exposure to excessive heat, the other a condition accompanied by hyperpyrexia. In the former the body temperature must be maintained by warmth and stimulants, but the latter must be treated by methods to reduce the temperature. Heat stroke may be the result of excessive work in unsuitable clothing. In a moist tropical country there is more danger of heat stroke than in a hot dry climate.

**Fever.** When the heat-regulating centres are deranged by disease the body temperature usually rises, yet the patient feels cold and shivery. This effect is brought about by failure of the heat loss to keep pace with heat production, although the rise of body temperature will tend to cause an increased loss of heat. The skin is dry, showing that the activity of the sweat glands is decreased. When sweating occurs the temperature falls. The cause of fever is generally a toxin, probably of bacterial origin.

When the body temperature rises the rate of chemical changes will be increased, and there will be excessive breaking down of tissues with rapid loss of weight.

That the heat-regulating centre is defective in its action is shown by the tendency for the temperature to fluctuate in fever.

**Ventilation.** The object of ventilation is to furnish a supply of fresh air, mainly to help in regulating the body temperature. The chemical impurity of the air in a "stuffy" room does not make much difference to the processes of respiration; an increase in carbon dioxide in the air merely increases the respiratory ventilation of the lungs, and it is only with excessive amounts, i.e. over 1 per cent., that headache or other unpleasant symptoms result. The decrease in amount of oxygen which occurs when a room becomes close is much less than that which can be tolerated elsewhere without ill effects. The proof for this is best shown by an experiment by Leonard Hill, on students who volunteered to remain in a large box. When the students became uncomfortable another student outside breathed the air in the box through a tube and he felt no ill effects. If the students inside breathed fresh air through tubes they still felt uncomfortable, but if a fan was turned on so that the air in the box was set in movement the feelings of discomfort disappeared.

It is the moisture of the air which makes it uncomfortable, but if the air is caused to move so that evaporation is increased the discomfort diminishes: thus we see that one factor in ventilation is to produce air movements. Fresh air has an effect in diluting the number of bacteria present in a given space: this is an additional reason for ventilating with fresh air and not merely by causing movements of the air in a room.

Experiments to show that expired air contains toxic substances were at one time said to be successful. The effects produced were due to the relatively large amount of material injected, and it is now believed that the effects of ill-ventilated rooms are not due to volatile toxins.

**Changes in Barometric Pressure.** At high altitudes the barometric pressure is less. The decrease in pressure as such has no effect on the animal body because it is distributed equally by the liquids in the body so that no pressure differences exist. The effect of a high altitude is due to the decrease in oxygen pressure. The percentage composition of the air is practically uniform, hence the oxygen pressure diminishes in proportion to the barometric pressure. If the oxygen pressure falls the saturation of haemoglobin with oxygen decreases, therefore the capacity to do work is diminished owing to a lesser supply of oxygen in the blood.

*Mountain Sickness.* When people ascend to a high altitude they may suffer from headache, nausea and vomiting, and the volume of air breathed is increased. The symptoms, which diminish later on, but return when exercise is taken, are due to lack of oxygen, and the individual may be cyanotic. The lack of oxygen stimulates the respiratory centre or makes it more sensitive to carbon dioxide, hence there is a slight fall in the carbon dioxide tension in the alveoli. As the carbon dioxide is maintained near to the normal tension the percentage of carbon dioxide in alveolar air must rise with the decrease in barometric pressure. The symptoms due to lack of oxygen will occur more readily when muscular exertion takes place, hence their onset is related to the amount of exercise taken, and to the physical fitness of the individual.

A high altitude is more rapidly reached in an aeroplane than when ascending a mountain, but the exertion will be much less. The first symptom in an aeroplane or balloon may be sudden loss of consciousness. Lack of oxygen interferes with the normal action of the brain. Great obstinacy and irrational behaviour may result from anoxæmia.

On remaining at a high altitude the symptoms of mountain sickness decrease. This adaptation might be due to secretory activity of the lung epithelium (see p. 281), but such secretion is doubtful. There is a change in the oxyhaemoglobin dissociation curve which facilitates the exchange of oxygen at low pressures, but this change is probably not due to an increased acid formation in the blood. At least lactic acid is not found in the blood at high altitudes.

An important compensatory process is an increase in the amount of haemoglobin in the blood. The blood first of all becomes more concentrated. Then there is an increase in the number of cor-

puscles per cu. mm. as well as an increase in the total amount of haemoglobin in the blood.

This increase in haemoglobin persists for a week or more, after returning to a lower altitude. Breathing oxygen mitigates the effect of decreased barometric pressure. By the use of oxygen airmen can fly at higher altitudes. Even in mountain climbing it is found that at very high altitudes the beneficial effect of oxygen more than compensates for the extra weight to be carried in the form of oxygen cylinders.

**Effect of Increased Atmospheric Pressure: Caisson Disease.** Increased atmospheric pressure occurs in certain

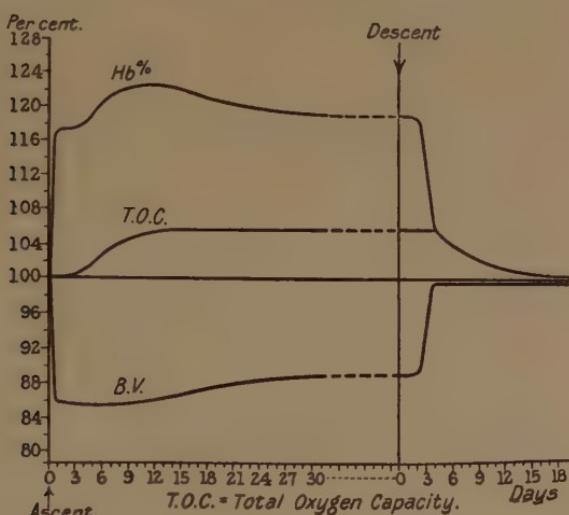


FIG. 299.—Effect of High Altitude on Blood (Dreyer and Walker).

The first effect is a loss of plasma, hence the blood volume (*B.V.*) decreases and the percentage of haemoglobin (*Hb%*) increases. Later on the total oxygen capacity (*T.O.C.*) increases owing to an increased formation of haemoglobin.

industrial processes. Divers are subjected to a high water pressure; they must, therefore, have air supplied to them under pressure. In tunnelling through soft ground air pressure is used to support the tunnel until the walls can be made firm.

After working under these conditions men may develop symptoms consisting of pains or paralysis, and even death may occur. These symptoms are not due to the oxygen or carbon dioxide of the air. Excess of oxygen does not cause symptoms until the pressure of oxygen exceeds that of two atmospheres, when subsequent inflammation of the lungs leading to pneumonia may occur. Such pressures would only be obtained when the atmospheric pressure is raised to about ten atmospheres. As caissons are not

worked at such high pressures the effect of excess of oxygen need not be considered further.

When exposed to a high atmospheric pressure the blood becomes saturated with the gases at the pressure at which they exist in the lungs. The extra amount of oxygen dissolved is small compared with the amount taken up by haemoglobin. The pressure of carbon dioxide in air is so small that not much more will be dissolved when the pressure is increased. Moreover, the respiratory centre regulates the pressure of carbon dioxide in the alveolar air so that there is not much change in the pressure of carbon dioxide in the blood.

The increase in pressure of nitrogen causes a much larger amount to dissolve in the blood. If time is allowed for saturation to occur the whole body will become saturated with nitrogen. Nitrogen



FIG. 300.—Photograph to show Gas Bubbles in Arteries and Veins of Intestines after Rapid Decompression (V. Schrötter).

is about five times as soluble in fat as in water, and therefore large volumes of nitrogen may be dissolved in the body. On suddenly releasing the pressure this nitrogen can come off as a gas. The gas may block the blood-vessels, thus causing stoppage of the circulation. If the gas is disengaged in a delicate structure, the latter will be damaged. The symptoms that result will depend on the part of the body in which the gas is set free. Damage to the nervous system is naturally the most dangerous. To prevent the symptoms the workers in compressed air must not be decompressed suddenly. If the pressure of the air is decreased by half it is found that the gas does not come out of solution. A super-saturated condition results and the gas comes off rapidly through the lungs.

After some time at this pressure the pressure may be halved

again. When the pressure has been reduced to two atmospheres it is safe to reduce it to atmospheric pressure. Works carried out with the use of compressed air are provided with air chambers in which the workers are decompressed.

This method of decompression by stages gets rid of the excess of nitrogen more quickly, and with less danger than if the pressure is reduced at a uniform rate. In the latter case the difference in pressure is small at first so that very little nitrogen escapes, but as the pressure falls the difference becomes greater and greater until liberation of nitrogen bubbles may take place. During decompression it is advisable that exercise be taken. This increases the rate of the circulation, therefore removing nitrogen more rapidly from the tissues. The pressure of nitrogen in the blood can be followed by collecting samples of urine, pumping off the gases by a mercury pump and determining the amount of nitrogen which had been dissolved in it. If symptoms of caisson disease occur the only remedy is to recompress the patient in the hope that the bubbles will redissolve before they run together to form large nitrogen bubbles. Therefore a medical lock is necessary in which workers can be recompressed if any symptoms of compressed-air illness occur.

**Asphyxia.** Lack of oxygen may result from a number of causes. Low barometric pressure has been studied above. If the lack of oxygen is due to inability of the blood to carry oxygen it is known as *anoxæmia*. Anoxæmia may result from lack of haemoglobin (*anæmia*), or from the haemoglobin being combined with some other substance, e.g. *carbon monoxide poisoning*. When the respiratory exchange is obstructed the condition of asphyxia results. This implies not only a progressive lack of oxygen, but a progressive increase in carbon dioxide. The symptoms start with increased attempts at respiration, an increased force and frequency of the heart, and a rise of blood pressure. The blood becomes reduced so that the exposed parts appear purplish (cyanotic). This first stage lasts about one minute. The second stage is marked by violent and convulsive attempts at respiration. The blood pressure remains high because of vaso-constriction, but the heart-beats are decreased in frequency. The third stage is a failure of all the vital processes. The respiratory movements become feeble and infrequent, the convulsions die away.

The blood pressure falls because of failure of the heart. Heart-block occurs first as a 1 : 2 rhythm, then 1 : 3, and finally complete heart-block takes place. The pupils are dilated: the sphincters are relaxed, urine and faeces being passed involuntarily.

During asphyxia Traube-Hering waves may be seen on the blood-pressure tracing. These are undulations of blood pressure which

occur at less frequency than the respiratory variations of blood pressure, and they are probably due to alterations in the activity of the vaso-motor centres. After death the right side of the heart, the veins and lungs are found to be engorged with blood whilst the arteries and left side of the heart are empty.

### BACTERIAL INFECTION: METHODS OF DEFENCE

Protection of the body against parasitic organisms includes such measures as those necessary to control mosquitoes and the intermediate hosts of worms, but we shall limit our description in this chapter to the mechanisms of defence against bacterial infections. These mechanisms are a series of balanced reactions between the tissues of the host and the invading organism and they may lead to the destruction of the parasitic cells or to a neutralization of their toxins.

**Hæmolysins and Cytolysins.** If a rabbit is injected with the red blood corpuscles of a sheep which have been washed by centrifuging them with several changes of salt solution, and if the injection is repeated at intervals of about five days for about four injections, the following condition results. The blood serum from such an injected rabbit when mixed with the blood corpuscles of a sheep causes the sheep's corpuscles to break up or hæmolyze. The blood serum from an uninjected rabbit would have no such effect on the sheep's corpuscles ; we see therefore that the injection of sheep's corpuscles into a rabbit has caused the production by the rabbit of some substance which can destroy the red blood corpuscles from the same species as were those that were injected.

If the hæmolytic serum is heated to 55° C. for half an hour it will no longer cause hæmolysis, but its hæmolytic power will be restored by the addition of fresh serum from an animal whose blood need not be hæmolytic. Therefore we see that there are two factors required for the hæmolysis, one present in normal blood of all sorts and thermo-labile, i.e. destroyed by heating, which is called *complement* ; the other present in the blood of the injected animal and thermo-stable, i.e. more resistant to heating. This latter is specific as it is produced by the injection and is operative only on the red blood corpuscles of the species from which the injected corpuscles were obtained. This is called an *amboceptor* because it links the complement to the antigen. The potency of these substances is very great ; it is possible to show the effect of the hæmolysis in dilutions of one in one thousand, whilst the amount of complement required depends upon the mass of corpuscles to be hæmolyzed. The substance which is injected to produce the immunity reaction is called an *antigen*.

If instead of red blood corpuscles one injects other cells the result

is the formation of a cytolysin. A haemolysin is merely a special example of a cytolysin.

**Precipitins.** If instead of injecting the rabbit with red blood corpuscles serum had been used, the rabbit serum would have acquired the property of producing a precipitate with the serum of the species from which the injected serum had been obtained. This reaction also depends upon the production of some specific substance. So specific is this reaction that if human serum were used for the injection a dilution of 1 : 1000 of the rabbit serum would still give a precipitate with a saline extract from a human blood stain. A slight reaction might be given at lower dilutions with blood of an allied species. This test is used as a test for the nature of a blood stain in medico-legal cases because an extract of the stain will produce a precipitate only when treated with serum from an animal which has been rendered immune to serum of the same species as that from which the blood stain is derived.

*The Biological Test for Blood.* The action of a precipitin in forming a precipitate with the proteins from an animal of the same species from which the injected blood was obtained is a delicate test for blood.

**Agglutinins.** Injection of foreign cells produces a reaction whereby substances are produced which cause the same kind of cells to collect together in clumps. Thus in the process of haemolysis clumping of cells may be seen to precede haemolysis. The main use made of agglutinins is in the diagnosis of bacterial species. The serum of an immunized animal will cause clumping of the bacterial species with which it has been injected in a dilution of one in one thousand or one in ten thousand, but will not cause agglutination of allied species in nearly such high dilutions.

**Anti-toxins.** When a bacterial toxin is injected into an animal, if the dose is not sufficient to kill the animal an anti-toxin is produced, i.e. some substance which can neutralize the effect of a toxin. For instance diphtheria antitoxin is made by injecting diphtheria toxin into horses, some time after which the horse is bled and the blood allowed to coagulate. The serum from this clotted blood is used to protect people from the action of the bacilli of diphtheria.

**Opsonins.** Leucocytes can ingest bacteria, but if the white corpuscles are separated from the serum and well washed by several changes of saline, they lose the power of phagocytosis. By adding some fresh serum to a mixture of washed corpuscles and bacteria, the bacteria are now taken up by the cells. Sera vary in their capacity for stimulating leucocytes, and this power is said to be due to some factor to which has been given the name of opsonin. By comparing the average number of bacteria taken up by the

leucocytes under standard conditions such as time, temperature and density of bacterial emulsion, the *opsonic index* can be determined. This is the ratio of the number of bacteria taken up per leucocyte, when the serum of the individual who is being tested is contrasted with that of a standard sample. The standard sample is usually the mixed serum from several normal individuals.

All the above mechanisms are protective : foreign cells are agglutinated and cytolysed. Foreign proteins are precipitated, and bacteria are ingested by leucocytes. These properties are increased by injection of the corresponding substances. In order to increase the resistance to bacterial infection one does not need to inject live bacteria and thus produce the corresponding disease, but one may use bacteria which have been killed by heat. The dead bacteria cannot develop and produce disease ; they may cause a slight febrile reaction by their contained toxins, but the immune bodies in the serum are increased in amount so that subsequent accidental infection may be resisted by the immunized individual. Such a suspension of dead bacteria is called *vaccine* and a dose of 1 c.c. containing several hundred million dead bodies is quite usual. Vaccination is a special case because although immunity is produced we do not know the infecting organism nor its relation to small-pox infection. Further, since the course of the vaccination suggests a typical growth process, it appears that the infecting organism is not dead and differs in this respect from bacterial vaccines.

By removing the fats from certain bacteria the process of immunization is facilitated. Bacteria like *Bacillus tuberculosis*, which contain a large amount of lipoid material, are difficult to stain. Once they have been stained they retain the stain even when washed with "acid alcohol." These bacteria are said to be "acid fast." Immunity to them is said to be brought about more rapidly if the lipoids are removed from the bacteria (Dreyer).

**Complement Fixation.** If a mixture of complement, amboceptor and antigen is made, it is found that the amount of antigen acted on depends on the amount of complement in the mixture. This suggests that complement is used up or altered in some way so that it ceases to be active. Unlike an enzyme, it is not capable of producing an indefinite amount of effect. The disappearance of complement in immunity reactions enables us to use red blood corpuscles as indicators for these.

If red blood cells are treated with inactivated serum from an animal immunized against that species of red blood corpuscles, the corpuscles are not haemolyzed, but take up the immune body. Such "sensitized" corpuscles can be washed by centrifugalizing and they will be haemolyzed by complement from any source. If

now a mixture of bacteria, complement and an anti-body be made, the complement will be attached to the bacteria if the anti-body is that for the corresponding species, but not if the anti-body is for a different species. Therefore if the mixture is incubated and added to "sensitized" corpuscles haemolysis will not take place in the former case as there will be no free complement, but it will occur in the latter as the complement will be free.

**The Wassermann Reaction.** There is a special diagnostic application of this process in the *Wassermann reaction* in which the three following mixtures are made :

| <i>Serum Inactivated by Heating.</i> | <i>Complement.</i>       | <i>Antigen.</i>   |
|--------------------------------------|--------------------------|---|
| A—From a case of syphilis            | + Fresh guinea-pig serum | + A suspension in saline of cholesterol and alcoholic extract of heart. |
| B—From a suspected case of syphilis  | + Do.                    | + Do.   |
| C—From a non-syphilitic case         | + Do.                    | + Do.   |

After these three have been incubated for a definite period of time, e.g. half-an-hour, sensitized red blood corpuscles are added. Syphilitic serum causes the complement to disappear in the presence of the antigen, hence no haemolysis will occur with *A*. Normal serum does not cause the complement to disappear, hence haemolysis will occur with *C* and haemolysis will or will not occur with *B*, depending on whether complement has not been or has been fixed. *B* is the test and it is said to be positive, i.e. indicating that the person from whom the serum was obtained has syphilis if haemolysis does not occur.

The amount of complement can be varied by using different dilutions of guinea-pig serum, so that by using a larger number of mixtures the relative amount of complement which has been rendered inactive can be determined : in this way it is possible to compare different degrees of activity in fixation of complement.

This reaction was devised on the assumption that it was an immunity reaction, and an alcoholic extract of the liver from a syphilitic foetus was used as antigen. Later it was found that extract of normal liver or heart, especially with the addition of a little cholesterol, will produce the same effect ; the reaction therefore does not depend upon the production of a specific antibody, but it is of great importance for diagnostic purposes.

**Anaphylaxis.** If an injection of a foreign protein is repeated with an interval of more than ten days between the two injections, the second dose is sometimes followed by collapse or death. This sensitization is known as anaphylaxis and the symptoms vary with

the species of animal into which the injection is made. It seems to be a condition of the body cells in which the foreign protein becomes attached to the protoplasm. One example of the anaphylactic condition is to inject a virgin guinea-pig with serum, later on kill the animal, remove its uterus and record its variations in tone. If now a small quantity of serum, from the same species with which the guinea-pig had been injected, is added to the saline solution surrounding the excised uterus, it contracts strongly and the excised uterus is frequently used as a test for the anaphylactic condition. In dogs another symptom is constriction of the bronchioles with asthmatic symptoms. Fortunately the condition is not usually fatal in the human subject, but asthmatic symptoms and coryza are sometimes due to a special substance such as grass pollen. A cutaneous erythema is produced by application of these substances to the skin and cutaneous reactions are used as a test for sensitiveness to special substances.

Anaphylaxis may be due to the presence of amboceptors in the cells. When the amboceptors are in the plasma the combination of the antigen with complement is harmless, but when the combination takes place in the cells violent activity occurs (Dale).

## CHAPTER XLII

### HEREDITY

The continuation of a species depends upon the reproduction of offspring resembling their parents. In the higher animals reproduction depends upon the union of the egg and the spermatazoon. The study of heredity can be approached from several different avenues; here we shall deal first of all with the results obtained when different varieties are crossed and afterwards consider what structural or chemical bases there are to account for the results.

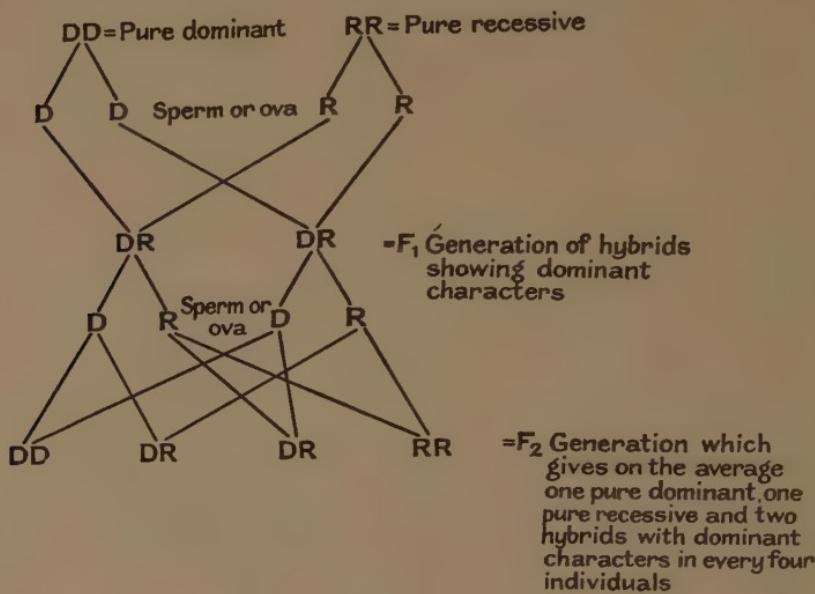
If two dissimilar varieties are crossed we may get fusion of some characters but not of others. Thus when Mendel crossed tall and dwarf peas the offspring might have been of intermediate height, but such fusion did not occur, for all the peas were tall plants. Tallness was the *dominant* characteristic here because it replaced entirely the opposite character of dwarfness. The latter character was not entirely suppressed because if the hybrid peas were self-fertilized it was found that the second generation contained 25 per cent. of peas, showing the *recessive* character of dwarfness, which bred true to this character. There were also 25 per cent. of the peas which bred true to the dominant character, whilst the remaining 50 per cent. were tall peas of a hybrid type, in so far that further breeding of these gave the same proportion of dominants and recessives as was given by the first generation of hybrids.

If we represent these characters by R for the recessive and D for the dominant we can construct a diagram showing the above relationships.

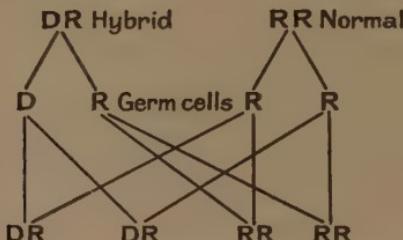
The simplicity of the above description only holds when we deal with two simple characters, but with a larger number of characters we find more complicated relations, for instance groups of characters may be inherited together. Occasionally, however, we find that some of the related characters do separate and this separation is known as "crossing over." Thus in animals a character which is generally associated with the male sex may be found in the female and the converse.

The application of Mendelian principles to human inheritance requires special consideration, but the experimental results are not of the same clear-cut character. Take, for example, the family studied by Farabee in which the peculiarity was that all the fingers

and toes had only two phalanges, like the thumb and big toe. This peculiarity was a dominant character. The matings, however,



were not between the hybrids, but between hybrid and normal individuals. As shown by the following schema this leads to a 1 : 1 relation in the individuals showing the peculiarity,



i.e. two hybrids showing dominant characters and two pure recessives which bred true to the normal character of three phalanges in fingers and toes. Colour-blindness and haemophilia may also be instances of Mendelian inheritance, but in the latter there are apparently some complicating factors. Certain inborn errors of metabolism behave like recessive characters which may be sex-linked.

In order to follow the subject further we must study the manner in which spermatozoa and ova are produced. The reproductive organs, like all the rest of the cells of the body, contain the inherited characters, and it is in this way that the inherited characters are passed on from generation to generation.

**Spermatogenesis.** The testes in the human subject consist of a number of coiled tubes contained between septa inside a thick coat of fibrous tissue. Each compartment between the septa contains several tubes each about 50 cm. long, which unite to form straight tubules leading into the vasa efferentia. The vasa efferentia unite to form the duct of the epididymis, a convoluted tube about 20 ft. long which leads into the vas deferens.

Spermatozoa develop in the tubes of the testes by division of the cells lining the tubules. The cells of the outer layer are large and they are called spermatogonia : these divide each to form two spermatocytes of the first order. Each of these divides to form



FIG. 301.—Photomicrograph of Testis ( $\times 100$ ).

One seminiferous tubule containing spermatozoa is seen. At the left lower corner a group of interstitial cells is visible between the tubules.

two spermatocytes of the second order, and finally each spermatocyte of the second order divides to form two spermatids. The spermatids undergo a change of shape whereby the cubical or round cell is converted into a spermatozoon. The transformation of a spermatid into a spermatozoon is as follows. A filament of protoplasm grows out to form the tail and the original cubical cell changes in shape. Most of the protoplasm is collected to form the middle piece, whilst the nucleus forms the head of the spermatozoon.

Amongst the spermatogonia are certain large cells which extend

inwards as large cones to reach the inner layer of cells. The spermatozoa collect round the ends of these and it is believed that they have a nutritive function. These are called cells of Sertoli or nurse cells.

During the process of spermatogenesis a type of cell-division is found which is called meiotic or heterotype division. The necessity for this type of division is that each species has a characteristic number of chromosomes in the body cells. When fertilization takes place if the spermatozoon and ovum each contained the adult number of chromosomes the fertilized egg would contain twice the normal number for that species. Hence reduction of the number of chromosomes to half must occur either before or after fertilization, and it is found that the reduction in number occurs before fertilization.

In the division of the primary spermatocyte we find that when

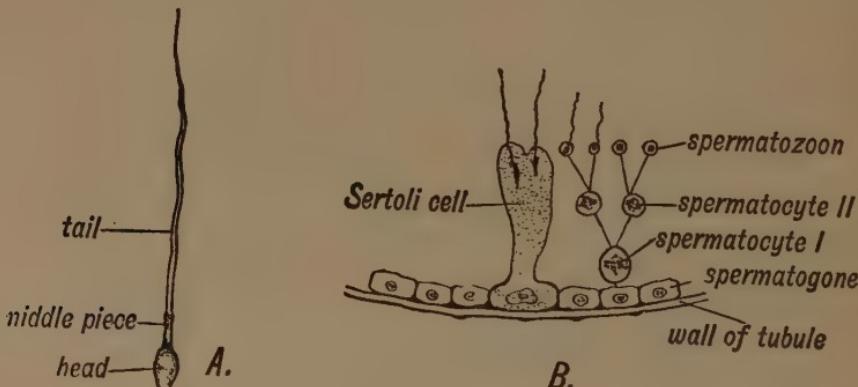


FIG. 302.—A. Diagram of a Spermatozoon. B. Diagram showing the Origin of Spermatozoa from the Lining Cells (Spermatogonia) of the Tubules of the Testicle (Keith).

the spireme breaks up into chromosomes, they become united in pairs. When these pairs become arranged round the equatorial plane of the spindle, instead of the chromosomes splitting, they separate again, so that each daughter cell (secondary spermatocyte) contains only half the normal number of chromosomes. The secondary spermatocyte now divides in the normal or homoiotype manner. Each chromosome, after reaching the equatorial plane of the spindle, divides longitudinally, so that each of the pair of spermatids receives the same number and kind of chromosomes as were contained in the secondary spermatocyte from which they arise.

As we shall see later it is the meiotic division without splitting of the chromosomes which is important in relation to the scheme of Mendelian inheritance described on page 553.

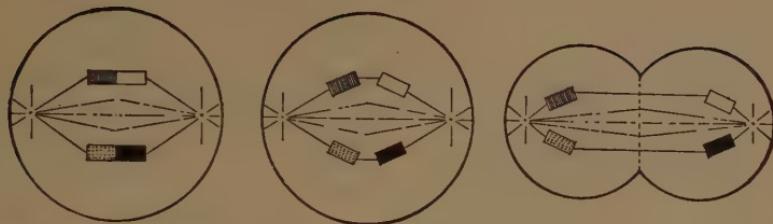


FIG. 303.—Diagrams to show the Distribution of Chromosomes to the Daughter Cells in the Meiotic or Reducing Form of Division (C. E. Walker's *Hereditary Characters*).

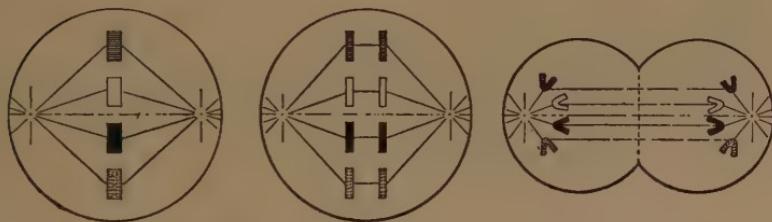


FIG. 304.—Diagram to show Distribution of Chromosomes to the Daughter Cells in the Ordinary or Somatic Form of Division (C. E. Walker).

**Maturation of the Ovum.** The ovary consists of a connective-tissue framework covered by an epithelial layer. In the foetus certain of the epithelial cells grow into the ovary in the form of columns of cells, which break up into groups of cells. One cell of a group increases in size whilst the others divide and form a mass of small cells surrounding the larger one. As the small cells increase in number they separate into two layers and the cavity between becomes filled with fluid. In this way Graafian follicles are formed ; in a section of an ovary these Graafian follicles in various stages of development may be seen. A fully developed follicle consists of a thickening of connective tissue surrounding the follicle, then a layer of small cells called the *stratum granulosum*. Inside the *stratum granulosum* is the *liquor folliculi*. At one side is a mass of cells called the *discus proligerus*, inside of which is seen the large ovum.

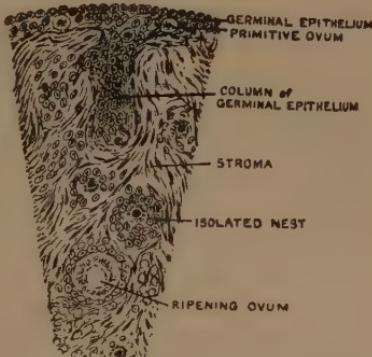


FIG. 305.—Diagrammatic Section of Ovary of Fifth-Month Foetus, showing Nests of Germinal Epithelium and Unripe Graafian Follicle (Keith).

Throughout the connective tissue of the ovary are cells, epithelial in form, called *interstitial cells*.

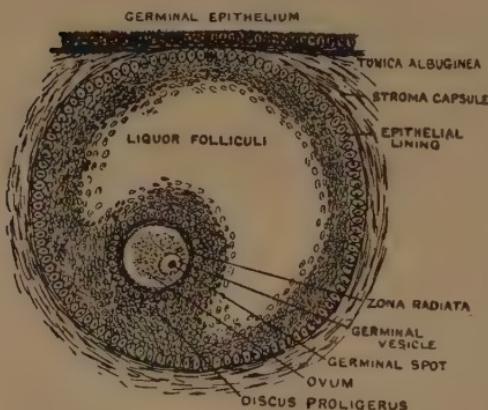
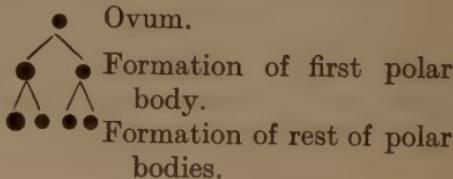
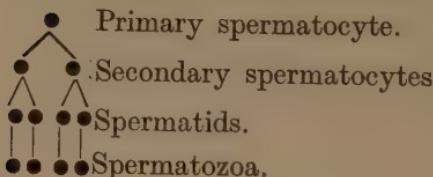


FIG. 306.—Ripe Graafian Follicle at Puberty (Keith).

large ovum is produced and the nuclei of what would be three other cells are extruded as "polar bodies."

Diagrammatically the differences can be expressed thus :



In the above description the human testes and ovary are described, but the process of reduction division is common to plants and animals.

**Mechanism of Heredity.** When the chromosomes of most cells are examined they are found to consist mainly of pairs of similar chromosomes. There are, however, certain chromosomes which are not pairs; they may be single chromosomes or two unequal chromosomes. The significance of these chromosomes that do not match is that when heterotype divisions occur the two daughter cells will differ in the types of chromosomes that they contain: in fact a segregation occurs as indicated by the D's and R's in the diagram of Mendelian inheritance (p. 554).

In some species an extra chromosome is associated with the male and in others an extra chromosome is characteristic of the female. In either case half the germ cells from one sex will contain the extra chromosome so that when crossed with the other sex cells half the fertilized eggs will give rise to males and half to females.

Just before fertilization the ovum divides twice. The first of these divisions is meiotic and a reduction in the number of chromosomes occurs. The second division is homiozygous. There is one great difference between the maturation divisions of the ovum and the process of spermatogenesis. In spermatogenesis each primary spermatocyte gives rise to four equal spermatids, but in the maturation of the ovum one

It is not necessary that sex be associated with an extra chromosome, but one of a pair of dissimilar chromosomes may determine the sex of the fertilized ovum.

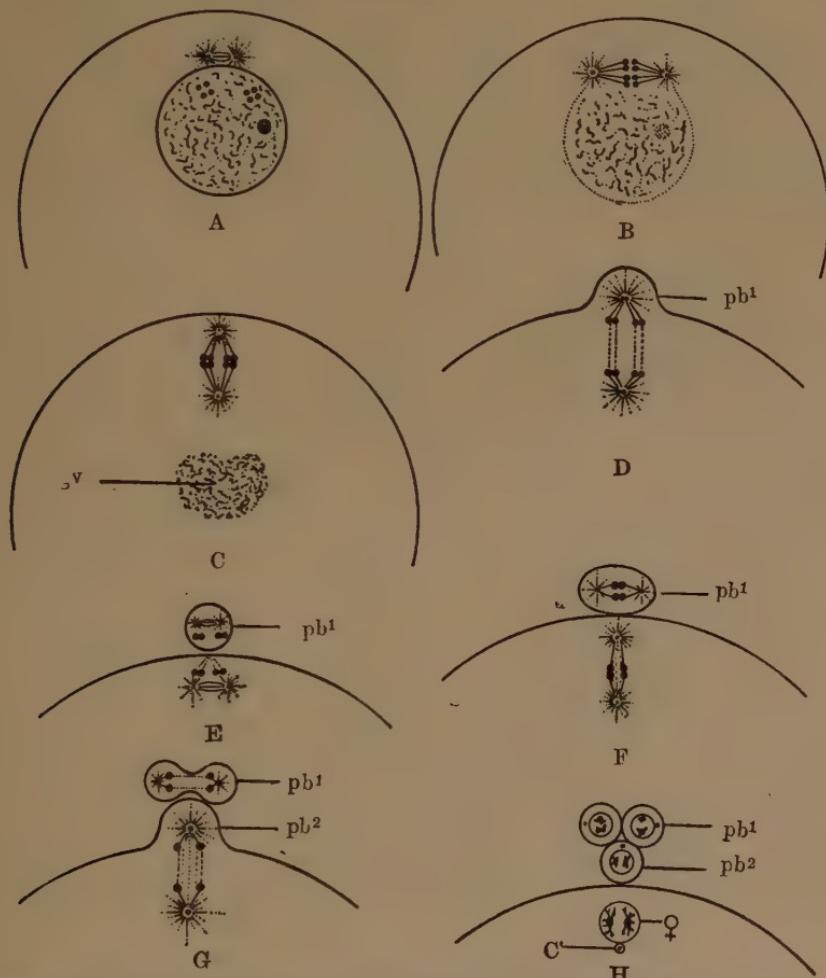


FIG. 307.—Diagrams showing the Essential Facts in the Maturation of the Ovum. The Somatic Number of Chromosomes is supposed to be Four (Flack and Hill, redrawn from Wilson's *The Cell in Inheritance and Development*).

A, Initial phase: two tetrads have been formed in the germinal vesicle. B, The two tetrads are in the equatorial plane of the mitotic spindle. C, The mitotic figure has rotated through 90°, leaving the remains of the germinal vesicle *gv*. D, Formation of first polar body (*pb*<sup>1</sup>). E, First polar body formed. F, Preparation for second division. G, Formation of second polar body (*pb*<sup>2</sup>) and division of first. H, Final stage: three polar bodies and egg nucleus (♀).

Mendelian inheritance shows that some inherited characters are associated with sex. If such characters be transmitted by the same chromosome that transmits the sex we can see that there will be an association between them.

By means of a long series of experiments it has been deduced that characters may be associated with definite chromosomes. It is found that in some instances linked characters are not inherited together but a "crossing over" occurs. The explanation of this is that when the chromosomes come together preparatory to the meiotic division, certain parts, instead of separating again, adhere together, so that after separation occurs the new chromosomes are formed of part of each of the original pair and thus the grouping of the characters is altered. From the frequency with which crossing of related characters occurs the distance apart in the

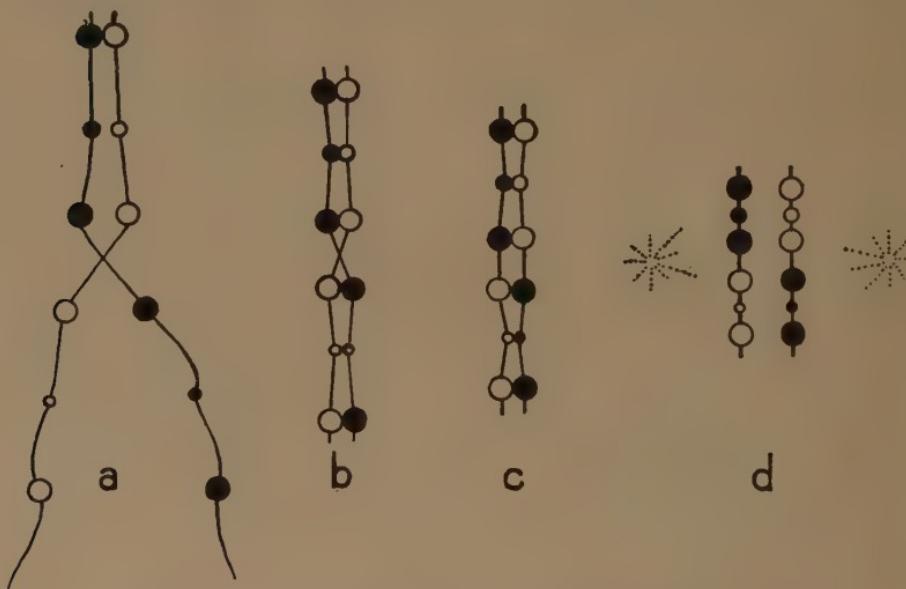


FIG. 308.—Diagram to illustrate the Possible Mechanism of Crossing of Characters (Morgan, *Proceedings Royal Society*).

a, b = chromosomes lying across one another, c = result of splitting of the chromosomes and union of the non-corresponding fragments, d = subsequent arrangement in cell division so that the daughter cells receive an abnormal segregation of genes. Crossed chromosomes have been seen in histological specimens, but the division and union is hypothetical to agree with the observed facts of crossing of characters.

chromosome of the "genes" for these characters has been mapped out.

Although a great deal of evidence is in favour of the chromosomes being the means whereby characters are inherited one must not forget the possibility that the protoplasm of the cell may also have an influence on the subsequent development. Chemical substances carried in the blood may also affect the germ cells. For example, alcohol and the toxin of syphilis are said to injure the germ cells. That normal chemical substances of the nature of hormones may act upon and alter germ cells so that acquired characters may be inherited is maintained by Cunningham.

**Process of Fertilization.** Fertilization occurs when the spermatozoon enters the egg. The head and middle piece enters but the tail is no longer required. The nuclei of both the male and the female cell undergo the preliminary processes of division and the chromosomes become arranged round the equatorial plane of a single spindle. They then divide in two so that two daughter cells are formed, each containing the number of chromosomes characteristic of the species and each having identical chromosome characters. As all the body cells will be the same the reproductive organs when they develop will contain the inherited characters so that segregation does not occur until reduction division occurs again.

Usually only one spermatozoon enters each ovum although many may congregate round it. In fact there seems some chemical attraction for the spermatozoa. One reason why only one spermatozoon enters is that a membrane is formed round the fertilized ovum. This membrane is best seen in marine eggs such as those of the sea urchin. Here in addition to fertilization by spermatozoa many other influences, such as exposure to dilute acid followed by return to normal sea water, will cause the formation of a fertilization membrane and perhaps development of the egg.

The spermatozoa are attracted to the egg by a chemical sense called *Chemotaxis*. If capillary tubes containing dilute reagents are brought into contact with a drop of solution containing spermatozoa of the fern, it is found that the spermatozoa congregate near some of these tubes but desert others. Malic acid is one substance which has a marked positive chemotactic influence (Pfeffer).

Similarly capillary tubes which contain sea water which has been in contact with ripe sea urchin eggs become crowded with spermatozoa when placed in sea water containing the spermatozoa from the same species.

Once one spermatozoon enters the ovum, others are prevented, and there are now two pronuclei present, male and female. These undergo the preliminary stages of division and approach each other. The achromatic spindle is formed from the achromosome which is carried

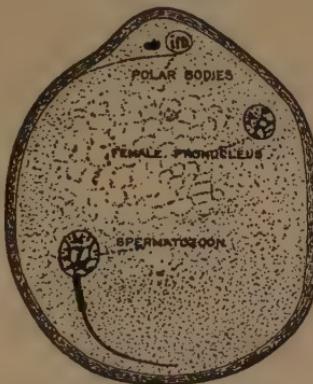


FIG. 309.—Mature Ovum of a Bat, showing the separated Polar Bodies, the Female Pronucleus and the Formation of the Male Pronucleus from the Head of the Spermatozoon (Keith, after Van der Stricht).

In this case the tail-piece has not been left behind.

by the spermatozoon. The chromatin from both male and female pronuclei becomes arranged on the spindle and they split so that two daughter nuclei are formed, each containing chromosomes equally provided by the male and female pronuclei. The ovum then divides into two equal cells.

If these two cells are separated each may form a separate complete individual. Later on, with increase in their number the cells become specialized, so that each will not form a complete individual.

**Determination of Sex.** The sex of the individual is in general determined at fertilization. This statement is based on the fact that certain special chromosomes are associated with male or female individuals. When reduction division occurs the special chromosome will pass into half of the sex cells ; therefore on fertilization half the individuals will contain the special chromosome which will thus cause half the individuals to be of the sex which this chromosome represents. Any other characters borne by genes in the sex chromosome will show sex-linked inheritance except for an occasional crossing over as described above.

Special conditions exist in special communities. Thus in bees the majority of individuals are female workers. The explanation of this is that unfertilized eggs give rise to drones and fertilized eggs to females. A few of the females are fed on a special diet which causes them to develop into fertile females (queens), whilst the others on a poorer diet develop into sterile females (workers).

TABLE LXIII  
DIET OF BEE-LARVÆ

| Food Constituents.    |   | Workers. | Queens. |
|-----------------------|---|----------|---------|
| Nitrogenous . . . . . | . | 51·21    | 45·14   |
| Fatty . . . . .       | . | 6·84     | 13·55   |
| Glucose . . . . .     | . | 27·65    | 20·35   |

The development of sex depends upon hormones from the testis or ovary. Thus it is possible to alter the sex of a chick by grafting a portion of the testis or ovary on to the developing embryo by making a hole in the eggshell.

The original impetus may be due to the chromosomes, but the development of the characters is due to the formation of the organs characteristic of the sex. In other words the chromosomes control the nature of sex gland which develops and the hormones from the sex gland determine development of the body into a male or female type.

In this chapter a brief sketch of Mendelian inheritance has been given. Many characters appear to be transmitted by special chromosomes which generally carry groups of characters. Crossing over of characters may occur in a certain proportion of cases. Sex is determined in some cases at least by a special X-chromosome.

NOTE.—For further information see T. H. Morgan, *The Physical Basis of Heredity* (Lippincott).

## CHAPTER XLIII

### REPRODUCTION

The commencement of the individual is the fertilization of an ovum by a spermatozoon, and in order that this may occur various devices are employed to bring the ova and spermatozoa together at the right time. Eggs and sperm may be distributed broadcast in the sea, but even so there seems to be normally some chemical attraction of the ovum for the spermatozoa.

**Site of Fertilization.** Fertilization occurs in the Fallopian tube or even in the abdominal cavity. This is shown by the occurrence of extra-uterine pregnancy where the placenta is attached to the tube or to some abdominal structure ; in such cases the developing ovum, if in the tube, ruptures it and serious haemorrhage results. Usually, however, the fertilized ovum reaches the uterus and becomes attached therein.

**Ovulation.** The ovum is set free by the bursting of the Graafian follicle in which it is contained. In the rabbit and guineapig it is said that the bursting is due to the swelling of the ovary by congestion as the result of copulation, and in general the female will only receive the male at the period of heat or rut.

In the human species ovulation is usually related to the menstrual cycle.

**Menstruation and Oestrus.** Menstruation is a periodic discharge from the uterus which occurs at intervals of about twenty-eight days. The changes that take place are comparable to those of the oestrous cycle in animals.

*The Oestrous Cycle* consists of four periods, namely proœstrum, oestrus, metoœstrum and anœstrum. The first period is marked by a congestion of the mucous membrane of the uterus, which in some cases may be terminated by a flow of blood from the vagina. The oestrus is the period of desire in the female during which she is willing to receive the male. If conception occurs oestrus is followed by gestation, otherwise metoœstrum succeeds, which is a gradual return of the generative system to the resting condition of anœstrum. In some animals, such as the dog, the anœstrous period is prolonged, oestrus occurring only once in six months. In other animals, such as ruminants, there is a breeding season, fre-

quently in the spring, in which several oestral cycles follow with a short interval between them, a prolonged anoestrus occupying the rest of the year.

*The Menstrual Cycle* starts from the resting condition of the uterus by a swelling and congestion of the mucous membrane. This is followed by extravasation of blood and the mucous membrane is shed, thus forming the menstrual discharge. Some observers state that the mucous membrane is shed entirely and regenerated from the epithelium of the glands.

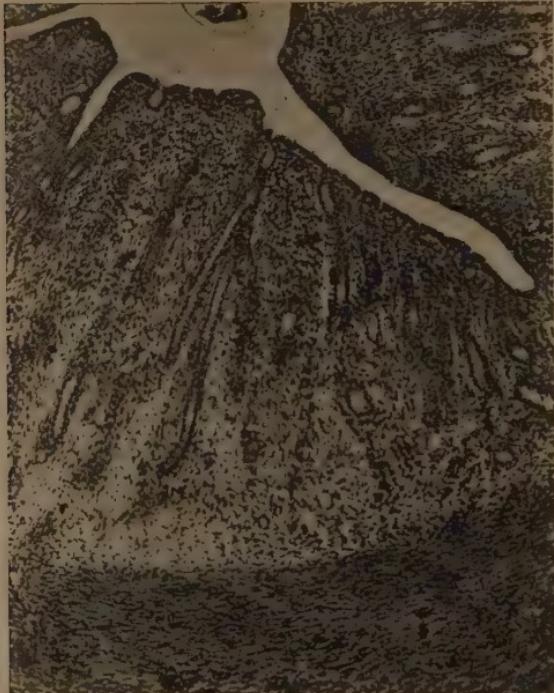


FIG. 310.—Photomicrograph of Cat's Uterus  
( $\times 88$ ).

Long glands are seen in the thick mucous layer and a portion of the muscular coat is seen below.

the human species insemination takes place by deposition of spermatozoa at the upper end of the vagina. The spermatozoa pass thence through the uterus to the Fallopian tube. The ability of the spermatozoa to travel by their own movements is shown by recorded cases where women have become pregnant when spermatozoa have been deposited at the vulva.

The mechanisms whereby fertilization is promoted depend upon depositing the spermatozoa as high up the female passages as possible before they have to rely upon their own activities.

**Erection.** This is a condition of turgor of the penis brought

Associated with menstruation are certain definite physical effects. Congestion of the uterus and adnexa may make them tender or painful and vaso-motor disturbances may produce emotional instability. A definite effect is also noticed on the temperature curve. The average daily temperature is about one degree higher before menstruation than after, thus there is a slow swing of the temperature curve up to the pre-menstrual period with a more rapid fall during menstruation to the post-menstrual condition.

#### Insemination.

In

by deposition of spermatozoa at the upper end of the vagina. The spermatozoa pass thence through the uterus to the Fallopian tube. The ability of the spermatozoa to travel by their own movements is shown by recorded cases where women have become pregnant when spermatozoa have been deposited at the vulva.

The mechanisms whereby fertilization is promoted depend upon depositing the spermatozoa as high up the female passages as possible before they have to rely upon their own activities.

**Erection.** This is a condition of turgor of the penis brought

about by distension of the sinuses by blood under pressure. By rendering the penis hard and large it can be inserted into the female passages and the spermatozoa deposited well up the vagina. In some animals (ruminants) there is a long whip-like prolongation which is believed to enter the os uteri and deposit the spermatozoa inside the uterus. Erection is brought about by dilation of the arteries and constriction of the veins, accompanied by relaxation of the smooth muscle of the erectile tissue. If the outflow were not retarded blood would escape too easily and erection would not result.

The nerve-centre for erection is in the lumbo-sacral region of the cord and the efferent nerves are the pelvic nerves (*nervi erigentes*).

Erection may occur after transverse section of the cord provided that the lumbo-sacral region is intact.

**Action of Uterus and Vagina.** There has been some discussion as to whether during coitus the uterus has a suction action drawing the semen into the uterus. It is possible that the muscles of the vagina contract, especially when it is filled by the penis, so that any contents will be squeezed into the relaxed uterus (Gunn). In bitches this contraction of the vaginal muscles is so marked that the dog's penis cannot be removed for some considerable time after coitus has ceased.

**Interval between Insemination and Fertilization.** Ovulation, or rupture of the Graafian follicle, occurs in some animals only at the time of insemination, but the time of ovulation in women is believed to be about twelve days after the menstrual period. If ovulation occurs only at this time and insemination occurs at other times there may be a considerable interval between the two. That spermatozoa may live for some time inside the female passages is known in the case of guineapigs, where live spermatozoa have been found in the Fallopian tubes fourteen days after insemination. Longer intervals are known amongst other animals, e.g. in bats the spermatozoa remain alive all the winter in the female passages. In bees, where the queen is in-



FIG. 311.—Photomicrograph of Erectile Tissue ( $\times 67$ ).

Note spaces, distension of which by blood produces erection.

seminated on one occasion only, the spermatozoa are kept alive for a long time.

Spermatozoa live longer in semen than in salt solution and it is probable that the secretions of the female genitalia may also help to keep them alive and active. It has been recorded that in women fertilization may be delayed for as long as twenty-four days after insemination.

**Implantation of the Ovum.** When the ovum is fertilized it commences to divide; it passes along the Fallopian tube and is usually arrested at the fundus of the uterus, where it becomes

attached by its velle to the mucous membrane. These folds grow up to close over the ovum, thus forming the decidua.

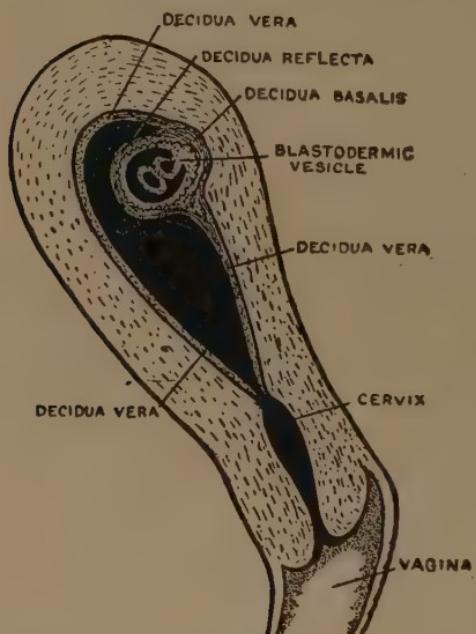
From the surface of the ovum the chorionic villi grow and penetrate into the mucous membrane, probably by a process of digestion of the tissues.

The villi, which grow into the decidua reflecta atrophy later, but those which grow into the decidua basalis ultimately form the placenta. This process of implantation depends upon an internal secretion of the corpus luteum in the ovary. At least, injury to the corpus luteum in the early stages of pregnancy usually causes abortion.

FIG. 312.—Section of Uterus showing in Diagrammatic Manner the embedded Ovum and the Differentiation of the Decidua into Three Parts (Keith).

**Corpus Luteum.** When the Graafian follicle ruptures and the ovum escapes haemorrhage occurs into the cavity of the follicle. The cells of the membrana granulosa multiply and grow into the blood clot, so that ultimately the cavity is filled with a mass of large cells which give a yellow colour—due to carotin—to the whole.

When pregnancy does not occur these corpora lutea atrophy within a month or two, but if pregnancy occurs they grow larger and remain for some months. Removal of the corpus luteum generally prevents the implantation of the ovum, and in a non-pregnant woman removal of the corpus luteum causes menstruation to occur. In some animals the corpus luteum may grow and a



pseudo-pregnancy results. In this condition many of the phenomena of pregnancy may occur, such as development of the mammary glands and secretion of milk.

**Placenta.** The villi which grow into the decidua basalis grow into a blood space and by their multiplication form the placenta. The structure of the placenta is thus a blood space filled by a mass

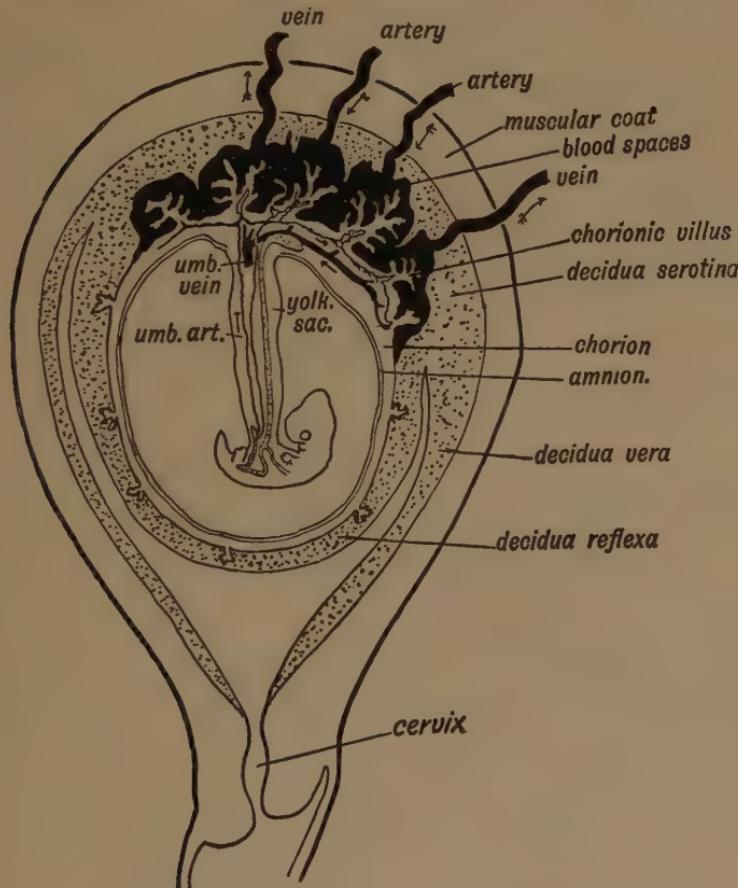


FIG. 313.—Showing Arrangement of the Amnion, Chorion and Decidua in the Third Month and the Formation of the Placenta (Keith).

of villi composed of a syncytium and containing the foetal blood vessels; the maternal blood is separated from the foetal by the syncytium covering the villi.

During intra-uterine life the placenta plays the part of the following systems of the adult—alimentary canal, lungs, and excretory system; in fact all exchanges take place between the foetal and maternal blood in the placenta. In addition the placenta acts as

a storehouse as it contains a considerable deposit of glycogen.

The presence of the placenta is associated with peculiarities in the circulation of the foetus. The fact that the maternal and foetal blood are separated by a membrane may account for the prevention of transfer of bacteria from the mother to the foetus whilst allowing the passage of anti-toxins, etc., to the offspring.

The development of the ovum to embryo and foetus is dealt with in text-books of embryology ; here we are concerned only with the physiological functions of this development ; and in connection with birth the foetal circulation is of considerable importance.

**Fœtal Circulation.** The two umbilical arteries extend from the internal iliac arteries to the placenta. After exchange of materials in the placenta the blood returns by the umbilical vein,

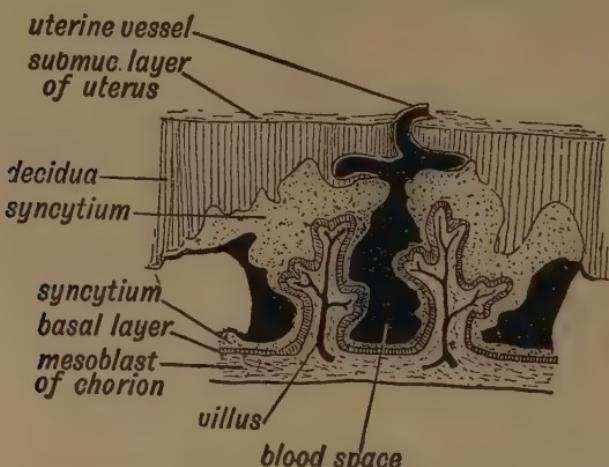


FIG. 314.—Diagrammatic Section of the Decidua Serotina (formed from the Mucous Membrane of the Uterus) and Chorion to show the Manner in which the Placental Blood Spaces are formed (Keith).

which on entering the abdomen runs upwards to the liver where it divides into two branches. The larger branch is joined by the portal vein and enters the liver : the smaller continues as the *ductus venosus* to the inferior vena cava. The arterialized blood mixed with the venous blood coming up by the inferior vena cava enters the right auricle and is directed by the Eustachian valve through the foramen ovale into the left auricle. From the left auricle it passes to the left ventricle and aorta, thence by the carotid and subclavian arteries to the head and arms. This supply of arterial blood facilitates the more rapid development of the head, which is relatively more developed at birth than the legs. The venous blood returning from the head and arms passes through the right auricle to the right ventricle and pulmonary artery. As very little blood passes to the lungs most of it passes through

the *ductus arteriosus* to the aorta, where it is joined with some arterialized blood left over from the head and arms to pass down to the lower extremities and abdomen.

One of the important consequences of birth is the alteration of the circulatory system to the adult form.

**Birth.** At the end of a period of about two hundred and eighty days after fertilization birth occurs. The cause of this phenomenon is unknown. To understand the processes that take place at birth one must make a careful study of the mechanics of the passage of the foetus from the uterus through the vagina, which study is an integral part of the subject of midwifery. At this stage it is sufficient to point out some of the salient points.

The foetus is expelled from the uterus by contractions of its muscular wall combined with relaxation of the neck of the uterus. This is followed by forcing the foetus through the vagina and vulva, during which the head of the foetus has to pass through the pelvic cavity, which is barely larger than the foetal head. Needless to say the tremendous distension of these passages has been preceded by a process of softening extending throughout the greater part of pregnancy ; in spite of this preparation the stretching is accompanied by great pain (labour pains).

There are also effects produced on the circulation of the blood in the foetus. Contraction of the uterus interferes with the circulation in the placenta and the umbilical cord is in danger of being compressed between the walls of the pelvis and the foetus.

**Changes at Birth.** After the child is born the placenta separates from the uterus and henceforth the child must depend upon its own resources for oxygen, heat maintenance, nutrition and excretion, instead of being maintained in an incubator at a uniform temperature and provided for in every way through the placenta. This is a cataclysm for the newly-born infant.

The most urgent requirement of a new-born infant is the establishment of gaseous exchanges. The circulation through the placenta stops mainly by the contraction of the walls of the umbilical arteries, probably brought about by the influence of cold air. The blood from the placenta drains into the foetus aided by any pressure exercised on the placenta by the uterus.

The respiratory centre is aroused to activity by the increasing venosity of the blood, and if that does not occur reflex stimulation may start it. Cold air on the skin, or even mechanical stimulation of the skin, may help to bring about respiration. If respiration does not occur artificial respiration may be necessary.

Once respiration occurs the child cries and the lungs become gradually distended, changing from the foetal to the adult condition. The foetal lung is solid and glandular whilst the lung after birth

contains air. An important distinction between the lung of a child which has been born alive and one that died before birth is that the lung of the former contains air and will float if placed in water, like adult lung, whilst the latter sinks.

Associated with the expansion of the lungs is the increased flow of blood through the pulmonary arteries instead of some of it passing through the *ductus arteriosus*. It is not known how this change is brought about. There is always a possibility that mechanical kinking may be a factor as the expansion of the lungs will alter the relations of the parts in the thorax.

Cessation of blood flow through the umbilical vein follows the

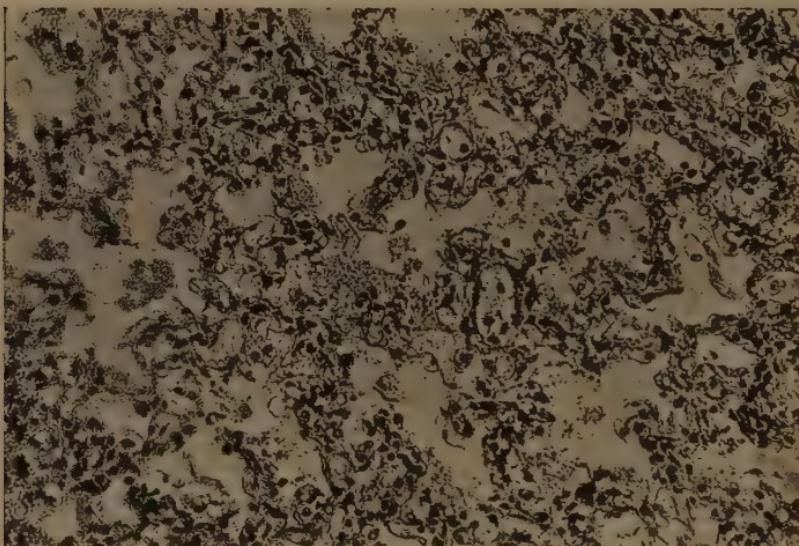


FIG. 315.—Photomicrograph of Foetal Lung ( $\times 100$ ).

Masses of cubical cells are seen surrounding spaces containing granular débris. On expansion the spaces are distended and the cells stretched out to form pavement cells. Contrast with Fig. 78.

stoppage of the circulation through the umbilical arteries and placenta. The *ductus venosus* is kinked by the liver being pushed down during respiration or closed in some other manner. With increased blood flow through the alimentary canal the amount of blood passing through the liver is increased. The liver swells and its functions are frequently upset. Owing to the decreased pressure on the right side of the heart, due to the lesser resistance in the pulmonary circulation than in the systemic circulation, the valve-like fold over the *foramen ovale* closes.

Within several weeks of birth the *ductus arteriosus*, *ductus venosus* and *foramen ovale*, are usually permanently closed. Thus the foetal circulation is transformed into the adult condition. Occa-

sionally the foramen ovale remains open, in which case the affected individual has a blue cyanotic colour (*morbus cœruleus*).

Less urgent than the respiration, but equally important, is the maintenance of the body temperature. Warm surroundings are essential and in animals the mother keeps the young warm by huddling close up to them.

Digestion and excretion must also commence, and jaundice is a frequent sequence to birth, possibly due to the change of the circulation due to larger amounts of blood flowing to the liver through the portal vein.

**Pregnancy.** The physiology of pregnancy is beyond the scope of this book, but the following obvious points must be mentioned. The uterus must enlarge as the foetus grows : this is accomplished by an increase in size of the individual muscle-fibres. The increase in size of the uterus and its contents will interfere with the downward movement of the diaphragm, hence costal breathing becomes more pronounced. The increased weight towards the front of the abdomen will be balanced by holding the shoulders backwards (a physiological lordosis) : in order to maintain the balance of the body the lordosis is more pronounced in short women.

As the mother must supply the foetus, in addition to herself, with oxygen and building materials and must, in consequence, get rid of carbon dioxide and other excreta, she will therefore show increased respiratory and excretory activity and she will eat a larger quantity of food. The foetus behaves as a parasite living on the mother as a host.

During the early stages of pregnancy the growing uterus may cause reflex effects, the most familiar of which is the well-known morning sickness commencing in the second month of pregnancy. Some of the changes, however, may be due to hormones ; the mammary glands for example develop even if the nerves to them are cut.

NOTE.—For further information the student should consult F. H. A. Marshall, *The Physiology of Reproduction*, Longmans, Green & Co.

## CHAPTER XLIV

### GROWTH

#### General Considerations

The volume of a cell is proportional to the cube of its radius whilst its surface is proportional to the square of the same. Therefore as a cell increases in size the surface area increases more slowly than its volume. If the metabolism per unit-volume remains the same there will be a limit, beyond which the diffusion of material into and out of the cell will not keep pace with the amount of metabolic change. By dividing the cell into two equal parts the total surface area of the two parts is greater than the surface area of the original cell. By this means further growth is possible. When a mass of cells is formed they interfere with each other as they are all competing for food materials, but a movement of liquid in their neighbourhood brings fresh food material and removes waste products. In multicellular animals movement of liquid is provided for by a circulatory system.

**Permeability of Cells.** In order that cells may live or grow exchange of material must occur between the cell and its surroundings. This elementary fact seems to be forgotten when the permeability of the cell is being discussed. The food materials consist of oxygen, water, amino-acids, glucose, salts, etc., and the waste products are carbon dioxide, water, simple nitrogenous substances, etc. The conditions which govern exchange of materials across a membrane (p. 161) are the same as those which control the passage through the surface of a cell. In membranes in the living body the substances passing through must go in at one surface and out at the other surface of the cells.

The permeability of cells is usually discussed in relation to inorganic ions. From studies on red blood corpuscles many authors conclude that the cell surface is permeable to anions, but not to cations. The evidence for this conclusion is that the inorganic constituents of cells do not seem to change in concentration when the composition of the solution outside of the cells is altered. There is no doubt that apparently cations do not readily pass into and out of cells, but some investigators have found an exchange of cations between red blood corpuscles and their surroundings. This

subject cannot be discussed in detail, but the student must recognize that if the cell surface is impermeable to cations there must have been a period in its growth when the cell surface was different. If cations could not enter the cell how did the potassium ever get into the red blood corpuscle? The solution of this conundrum is to recognize that the penetration of a substance into a cell may depend upon other factors than the permeability of the cell surface.

**Growth of Cells.** The growth of cells seems to be an inherent quality of the cells. In the absence of appropriate conditions growth cannot occur, or if the conditions are unsuitable abnormal growth may take place.

In the metazoa, growth of the ovum is usually initiated by fertilization although the occurrence of parthenogenesis must not be forgotten. After fertilization growth and cell division occur. Direct division is regarded as rare, and the usual form of division is that described on page 557 as the normal or homoiotype form of karyokinesis, in which the nuclear material breaks up into chromosomes. The chromosomes split, and each daughter cell receives the same amount of chromatin, and apparently exactly similar portions thereof. Thus each cell receives exactly similar hereditary characters. This view explains the continuity of the hereditary characters as all the cells of the developing organism will receive identical chromosomes, and therefore the germ cells when they develop will receive the same kinds of chromosomes that were in the original fertilized egg.

The differentiation of cells to form tissues and organs seems to depend upon contact with other cells. If the cells of a developing ovum are separated from each other, when only one or two divisions have taken place, each will give rise to a complete organism, thus showing the potentiality of each cell to form the organism. When cells have begun to differentiate it is found that they have lost the potentiality of reproducing the whole organism. Specialization of the cells causes a loss of this property. The various stages whereby the ovum is developed into the foetus are described in the study of embryology.

**Tissue Culture.** The effect of various conditions on cell growth can be studied in unicellular organisms, or by making cultures of growing tissues.

Under suitable conditions portions of embryonic material may be cultivated apart from the rest of the organism. Portions of the culture are taken out and transplanted under aseptic conditions into fresh media, and this process of transplantation is repeated at short intervals. By this method parts of tissues have been kept growing for a longer time than the natural duration of life of the species from which the culture was obtained. Thus we see that

mortality is not a necessary condition of the cell, but merely of the organism formed of various kinds of cells.

If epithelial cells of a glandular structure are isolated and grown they produce an inchoate mass of cells. If, however, some of the connective tissue cells are transplanted with the epithelial cells, definite tubules are formed (Drew). This experiment shows the influence of different kinds of cells on each other. In some way the development of the body is regulated so that each part grows to its own proper proportion. Secretions of the ductless glands may help in maintaining the proper balance of growth just as the connective tissue cells influence the glandular epithelial cells to form tubules.

Sometimes, however, a group of cells commences to grow in defiance of their surroundings. If this growth proceeds beyond a certain extent the cells break through such boundaries as basement membranes and invade other tissues. Such a type of growth is termed a malignant growth as it lives for itself and destroys other tissues.

We do not yet know why cells develop into malignant growths, but there are certain characteristic features about the cells of such growths. The cells, instead of being regular, tend to become irregular in size and arrangement. Frequently it can be seen that the normal type of cell division does not occur. Reduction in the number of chromosomes similar to the reduction that takes place in developing germ cells (Meiotic division) may take place. Instead of two poles there may be three or four poles to the achromatic spindle.

It is possible to produce similar irregularities in the size of cells, number of chromosomes and number of poles in developing sea-urchin eggs. Placing fertilized sea-urchin eggs in sea water to which a small quantity of alkali has been added induces cell divisions in many ways similar to those found in malignant new growths (Moore, Roaf and Whitley).

The above experiments are quoted to show that the development of the organism may be influenced by outside conditions. Normal growth requires the proper conditions. It may be that the ill effects of a lack of vitamins are caused through interference with the growth of some sorts of cells. Lack of vitamins can do this even in the adult, because some cells are being destroyed and renewed throughout life. A good example of cells which are being replaced during all stages of existence are the cells of the blood.

**Formation of Red Blood Corpuscles.** In the developing chick basophilic cells called angioblasts can be seen about the second day of incubation. These remain together in the form of a

syncytium which sprouts and unites with other masses to form plexuses. The contents of these cells liquefy to form plasma, but parts of the solid mass may remain and haemoglobin develops in these fragments. Some of the cells of the syncytium form the endothelium of the vessels, whilst others lie alongside this endothelium. The cells which project from the endothelium develop haemoglobin and divide to form red blood corpuscles. Thus we see that red blood cells can arise either from fragments of the liquefied syncytium, or at a later stage by division of certain cells in relation to the endothelium of blood-vessels.

The red blood corpuscles are formed in this way during early embryonic life in the yolk sac, liver and spleen. During later embryonic life red blood cells are formed in the bone marrow, but in the adult, formation of red blood corpuscles is limited to the bone marrow. The cells in the bone marrow which form the red corpuscles are nucleated and they contain a certain amount of haemoglobin. As they develop the haemoglobin increases in amount. Later the nuclei disappear before the cells escape into the circulation.

Any condition associated with lack of oxygen causes an increased formation of red blood corpuscles. Therefore at high altitudes, during chronic poisoning with carbon monoxide, after haemorrhage and when excessive destruction of red corpuscles has occurred, the bone marrow is stimulated to an increased formation of these corpuscles. During rapid formation of red cells some immature cells (called normoblasts) containing nuclei escape from the bone marrow into the circulating blood. When blood formation is abnormal large and small nucleated cells (called megaloblasts and microblasts), containing haemoglobin may be found in the circulating blood.

New-formed erythrocytes frequently contain a reticulum that can be stained : an increase in the number of these reticulated cells is looked upon as an indication of rapid formation of erythrocytes.

Formation of red corpuscles is, however, a continuous process, and does not occur only as the result of special conditions. The number of red cells in blood is fairly uniform, yet we have evidence in the excretion of bile pigments that red blood corpuscles are being destroyed continuously ; there must therefore be a continuous formation of them. The stercobilin of the faeces and urobilin of the urine are the end products of the bile pigments, hence the amounts of these pigments indicate the amount of destruction of red blood cells. It has been estimated that the erythrocytes last for an average period of thirty days.

**Formation of White Blood Corpuscles.** These are formed by mitotic division of previously existing cells and two views are held

as to the nature of these cells, namely (1) that red and white blood corpuscles are both derived from a common ancestor, and (2) that they are derived from several different types of cells.

The white cells are formed in the bone marrow, and the various lymphoid structures. If all the white cells represent stages in the development of one kind of cell the relative numbers of each variety would indicate the length of life of that stage just as the amount of any one of the products formed by radium-disintegration represents the rate at which that substance decomposes. It does not necessarily follow that all white cells are descended from one common ancestor. It is believed that the white cells may originate from a common ancestor, but that the final forms are turned out by special kinds of cells.

It is well known that variations in the relative numbers of white corpuscles occur under different conditions. For instance during digestion there is an increase in the total number of them, whilst bacterial infections are generally associated with a larger number of white corpuscles and with a relative increase in polymorpho-nuclear leucocytes. The hosts of animal parasites, e.g. intestinal worms, usually show a relative increase in the number of eosinophiles. Protozoal infections, such as malaria, are frequently accompanied by an increase in the relative number of large mononuclear leucocytes and transitional cells.

These variations suggest that there are either some reservoirs from which the various sorts of leucocytes may be liberated or that the formation of each special kind may be accelerated by different conditions.

In connection with white blood corpuscles it must be remembered that amœboid cells are also found in the connective tissues, one variety of which is known as clasmacytocytes, which may be identical with the large mononuclear and transitional white blood cells. Certain poisons cause changes whereby amœboid cells escape from the capillaries. The sequence of events is generally an increased flow of blood followed by adhesion of some white corpuscles to the wall of the blood-vessel. These white cells creep through the interstices between the cells and collect in the connective tissue (Waller). A later stage may be blocking of the blood flow and a collection of white cells so massed together that many of them die, forming pus corpuscles. This subject is treated more fully in pathology under the heading of inflammation.

**Nutrition and Growth.** In order that growth may occur the conditions necessary for maintenance described in Chapter XL. must be satisfied and therefore rate of growth is used as a means of testing the adequacy of a diet.

We do not know whether any special constituents are required

for growing individuals, but we know that an excess above that necessary for maintenance is required. Growth of tissue does not merely correspond to an accumulation of reserve material, but requires an expenditure of energy above that of the normal energy requirements of the body. It has been calculated that about 10 per cent. of the total energy of the food can be utilized for growth purposes.

Another consideration in relation to growth is the effect of size on the rate of metabolism. The body temperature being regulated within narrow limits, the heat production, apart from the performance of external work, will depend upon the rate of heat loss. As this rate is largely dependent upon the loss of heat from the surface of the body, the difference in temperature between the surface of the body and the layer of air in contact with it, and the extent of the surface are important factors in determining the rate of metabolism. The former of these two factors applies to the adult (see p. 532), but the latter makes considerably more difference in young (therefore small) animals than in larger ones.

The surface of an object compared with its volume varies with the shape of the object, and various formulæ have been evolved to express the surface area of man. The formula of D. and E. F. Dubois, is the one generally recognized as giving a close approximation to the surface area of the body, namely  $S.A. = 71.84 \times W^{0.425} \times H^{0.725}$  where S.A. = surface area in square metres, W = weight in kilos, and H = height in centimetres. The use of fractional powers is involved in the fact that weight is proportional to volume and density ; density being taken as uniform we see that the relation of surface to volume will involve a fractional power of the weight, e.g. :—

|                  | <i>Volume.</i> | <i>Surface.</i> | <i>Ratio.</i>             |
|------------------|----------------|-----------------|---------------------------|
| Sphere . . . . . | $(4/3)\pi r^3$ | $4\pi r^2$      | $3r^{2/3}$ or $3r^{0.67}$ |
| Cube . . . . .   | $a^3$          | $6 a^2$         | $6a^{2/3}$ or $6a^{0.67}$ |

The example given shows that a fractional power of weight and height may reasonably be expected in a formula relating weight to surface. Owing to the irregular shape of the body elaborate measurements had to be made to afford the data from which Dubois' formula was calculated.

The surface of the body was measured by making a cast of the surface. Thin clinging material impregnated with warm paraffin wax was fitted on the individual. After the wax had set the material was cut off and cut into small pieces, so that each was approximately flat. The pieces were all photographed, and those parts of the photographs representing the various pieces of the cast were cut out and weighed. At the same time a photograph

of a definite area was cut out and weighed, all the photographs being on paper of the same quality. By dividing the total weight of the photographs of the cast by the weight of the photograph of the standard area, the total area of the body was estimated. The area thus estimated agrees with the formulæ for calculating surface area from the weight and height of an individual.

In addition to surface area it is found that age and sex have an influence on metabolism, hence correcting factors for these are also necessary.

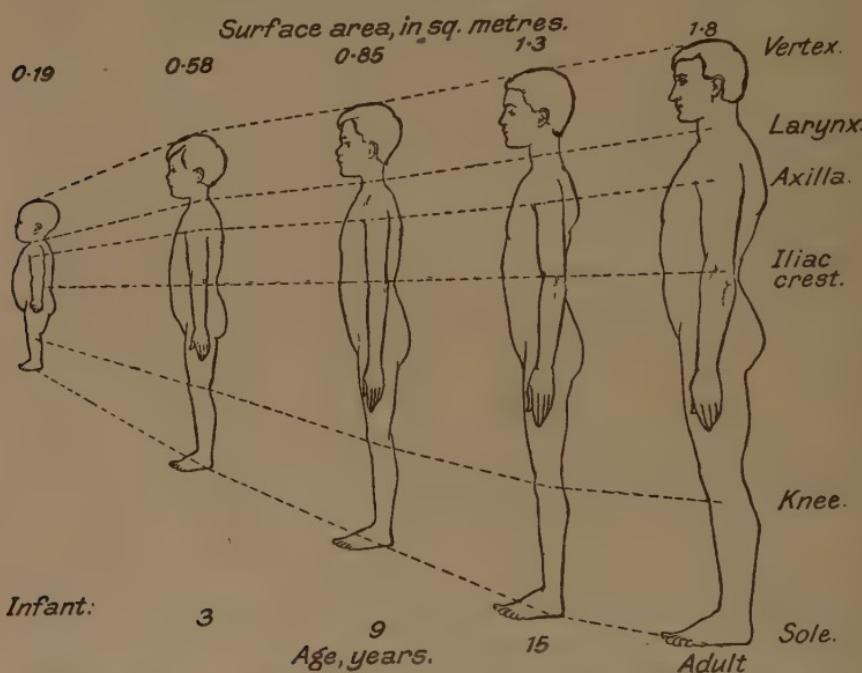


FIG. 316.—Sketch to scale (1/25) to show Proportional Growth of the various Parts of the Body (measurements from Vierordt's *Daten und Tabellen*).

The divergences of the interrupted lines show the proportional growth of the various sections. The slopes are not true rates owing to the unequal age intervals. Note the greater proportional growth of the limbs so that the relative length of the head decreases from about one-quarter to about one-eighth of the total length of body. The centre of gravity of the new-born infant is about the umbilicus, in the adult it is about the level of the anterior superior iliac spines.

Figure 316 shows the changes in the proportions of the various parts; the disproportionate growth of the rest of the body to the head is well shown.

The same disproportion in growth between the head and the rest of the body is shown in the following table from Vierordt (1903).

TABLE LXIV  
COMPARATIVE SIZES OF NEW-BORN AND ADULT STRUCTURES

|                                   | <i>New Born Infant.</i> | <i>Adult Male.</i> | <i>Ratio.</i> |
|-----------------------------------|-------------------------|--------------------|---------------|
| Weight in kilos . . . . .         | 3·1                     | 58                 | 1 : 19        |
| Length in cms. . . . .            | 49·5                    | 173                | 1 : 3·5       |
| Brain (weight in grams) . . . . . | 381                     | 1,428 (25 years)   | 1 : 3·7       |
| Liver . . . . .                   | 142                     | 1,801·3            | 1 : 12·7      |
| Heart . . . . .                   | 23·6                    | 301·7              | 1 : 12·7      |
| Kidneys . . . . .                 | 23·7                    | 302·8              | 1 : 12·7      |
| Spleen . . . . .                  | 10·7                    | 161·5              | 1 : 15·1      |

The rate of the heart-beat, and the rate of respiration vary with the age. For example Vierordt gives the following values for the pulse rate:—

|                                 |     |     |       |       |       |
|---------------------------------|-----|-----|-------|-------|-------|
| Age in years . . . . .          | 0·1 | 1·2 | 10·11 | 20·21 | 30·35 |
| Pulse rate per minute . . . . . | 134 | 111 | 87    | 71    | 70    |

The special requirements of growth are a plentiful supply of calcium and phosphate for the formation of bone, and a liberal amount of vitamins to ensure that the food materials are adequately used.

MILK. For a short period after birth milk furnished by the activity of the mammary gland is provided as a special diet for the young mammal. The composition of milk varies according to the nutritive requirements of the species for which it is intended. The relation of milk constituents to the rate of growth is shown in Table LXV.

TABLE LXV  
COMPOSITION OF MILK AND RAPIDITY OF GROWTH (PROSCHER)

| <i>Species.</i> | <i>No. of Days required to double the Weight at Birth.</i> | <i>Constituents of Milk.</i> |                        |                                    |
|-----------------|--|------------------------------|------------------------|------------------------------------|
|                 |  | <i>Protein.</i>              | <i>(per 100 parts)</i> | <i>P<sub>2</sub>O<sub>5</sub>.</i> |
| Man . . . . .   | 180  | 1·86                         | 0·033                  | 0·047                              |
| Horse . . . . . | 60   | 2·30                         | 0·124                  | 0·131                              |
| Cow . . . . .   | 47   | 4·00                         | 0·160                  | 0·197                              |
| Pig . . . . .   | 18   | 6·89                         | —                      | —                                  |
| Sheep . . . . . | 10   | 7·00                         | 0·272                  | 0·412                              |
| Dog . . . . .   | 8  | 8·28                         | 0·453                  | 0·493                              |
| Cat . . . . .   | 5  | 9·53                         | —                      | —                                  |

In addition to the proteins and salts the other constituents vary in concentration in the milk of different animals. The following table shows variations to be found in different kinds of milk.

TABLE LXVI  
COMPOSITION OF MILK OF DIFFERENT ANIMALS (IN PARTS PER HUNDRED)  
[PLIMMER]

|                   | <i>Human.</i> | <i>Cow.</i> | <i>Goat.</i> | <i>Mare.</i> | <i>Ass.</i> | <i>Whale.</i> | <i>Elephant.</i> |
|-------------------|---------------|-------------|--------------|--------------|-------------|---------------|------------------|
| Fat . . . . .     | 3·5           | 3·5         | 4·3          | 1·1          | 1·6         | 19·4          | 19·6             |
| Protein . . . . . | 1·5           | 3·5         | 4·6          | 1·9          | 2·2         | 9·5           | 3·1              |
| Lactose . . . . . | 6·8           | 4·8         | 4·0          | 6·6          | 6·1         | 0·0           | 8·8              |
| Ash . . . . .     | 0·2           | 0·7         | 0·6          | 0·3          | 0·5         | 1·0           | 0·5              |

Human milk contains less protein than cow's milk, and of that protein a larger proportion is lactalbumin. The ratio of lactalbumin to caseinogen in human milk is 60 : 40, whilst in cows' milk it is 15 : 85.

The specific gravity of cow's milk is from 1028 to 1035. When the fats are removed the specific gravity is increased in proportion to the amount of fat removed. Skimmed milk has a specific gravity of from 1033–1037.

Some of the constituents of milk are in solution, but the white appearance is due to suspended fat and to caseinogen. The globules of fat can be seen by the microscope, but even if the fat is removed the milk is still opalescent, due to the presence of calcium caseinogenate.

The main points about milk are the presence of caseinogen, lactose, fats, calcium and vitamins and its lack of iron.

*Caseinogen* is a phospho-protein which easily splits off phosphoric acid on warming with dilute alkalies. It contains a wide selection of amino-acids so that it is adequate both for growth and maintenance. It possesses the peculiar property of coagulating with rennin in the presence of calcium salts (see p. 180).

Coagulation of milk by rennin produces a jelly known as junket. On allowing this to stand the caseinogen with entangled fat shrinks and a fluid, whey, separates from the solid. The solid when suitably treated and ripened forms cheese which consists mainly of casein and fat. The liquid contains the other constituents of milk, and it may be used for the preparation of lactose. By adding a dilute acid (e.g. acetic) to milk the calcium is removed from the caseinogen which becomes precipitated, entangling the fat with it. One usually dilutes the milk with water before precipitating it in this way. The precipitate of caseinogen and fat formed during the bacterial souring of milk forms the basis of "cream" cheeses.

*Lactose.* Lactose is less readily hydrolyzed and absorbed than many other carbohydrates. It does not ferment by yeast and many bacteria produce acid from it. Perhaps one of the advantages of lactose is that it remains in the intestine and gives rise to acid by fermentation, whilst other carbohydrates are more rapidly absorbed. The organic acids thus formed interfere with the growth of putrefactive organisms, in this way exercising a useful function in the infant.

Lactose may be crystallized by evaporation of whey after removal of the lactalbumin. Addition of alcohol to the concentrated lactose causes it to crystallize.

*Fats.* When milk is allowed to stand the fats, being less dense than water, collect in a layer on the top. This layer is the cream

which can be separated, and on mechanical agitation of cream which has stood for several days so that its acidity has increased, the fat forms a semi-solid mass of butter. The peculiarity of butter fats is the relative absence of unsaturated fats with a comparatively large amount of acids of low molecular weight. It is these acids of low molecular weight which give the high Reichert-Miessl value in butter, i.e. the large amount of acids volatile during distillation in a current of steam, and also its relatively great solubility in glacial acetic acid.

*Salts.* The salts of milk contain all the inorganic ions required for growth with the exception of iron. The deficiency of iron is not important unless an exclusive diet of milk is continued for too long a time, as the liver of the new-born child contains a sufficient quantity of iron to last for the normal duration of milk feeding. The predominant inorganic constituent of milk is calcium.

*Lactation.* Milk is formed by the mammary glands which can exist in three physiological states, namely virgin, resting and active. As seen in Fig. 317, the virgin gland contains only a few tubules with an indication of saccular alveoli. The cells are columnar and stain deeply, and there is much connective tissue. The resting gland is more glandular than the virgin one, as it is a resting stage after having been active. It is composed of saccular alveoli with a lining of columnar cells. Inside the basement membrane are non-striated muscle cells, and the gland is divided into lobules by connective tissue stroma. As shown in Fig. 318 the active gland shows the following characteristics. The cells become spread out so that they are almost cubical in shape, whilst the alveoli become distended with the secretion which appears granular because of the suspended fat. The development of the glands occurs during pregnancy. The stimulus to their development is an internal secretion from the corpus luteum (see p. 571). Secretion of milk, however, does not occur until after the birth of the child and the activity becomes possible only after the removal of an inhibiting influence probably associated with the placenta. The first secretion contains many cells and is known as *colostrum*.

The quality of the milk depends upon the diet of the mother. Thus vitamins which cannot be formed by mammals must be present in the diet if a supply of them is to be maintained in the milk. Miss Hartwell has found that a diet containing too much protein is injurious to the offspring of nursing rats, but that this injurious effect is minimized by the addition of substances containing vitamin B to the mother's diet.

Caseinogen, lactose and fats are prepared in the mammary gland from constituents brought to them in the blood.

The basis for this statement is that caseinogen and lactose are



FIG. 317.—Photomicrograph of Virgin Mammary Gland ( $\times 100$ ).  
A few alveoli (or ducts) of darkly-staining cells are seen in a large amount of connective tissue.



FIG. 318.—Photomicrograph of Lactating Mammary Gland ( $\times 100$ ).  
The alveoli are distended with milk which appears like a foam structure owing to solution of the fat globules.

not found in the circulating blood. Fatty acids are found in blood, but the presence of a relatively large amount of fatty acids of low molecular weight in milk points to their formation in the gland.

### Physical Growth

Physical growth continues as an inherited growth impulse with the necessary corollary that a sufficient supply of energy and body-building substances is forthcoming. When growth is defective the various factors concerned must be considered. For instance it is not sufficient to say that the cause of the deficiency is in defective action of a ductless gland. We must consider whether the ductless gland is defective because it suffers from lack of power to carry out its functions in a normal manner or whether it is defective because of a lack of the necessary raw material for its activity. These may be a matter of degree as one organism may require a larger supply than another, but so long as this extra amount is furnished growth is not impeded.

The early stages of growth consist of a calcification of bone, and an increase in muscle, leading to a gradual acquirement of the adult form. The process of calcification requires a plentiful supply of calcium and phosphates as well as such constituents as vitamin A.

*Puberty.* When the growth has reached a certain stage puberty occurs. This is a period of growth during which the sexual characters become more marked. Hair grows on the pubes and armpits and in the male on the face. The voice changes in the male. In the female menstruation commences, the pelvis tilts and the breasts become larger. It is said that the breast development is mainly fat to prepare for the growth of the gland, but that growth of the glandular tissue is not marked until pregnancy occurs.

After puberty changes are less marked. Gradual growth occurs until a maximum development is reached. With advancing age metabolism becomes less intense, and there is a tendency for fibrous tissue to develop and for lime salts to become deposited. The effect of presbyopia where the lens becomes more rigid, and does not so easily accommodate for near objects, and the sclerosis of arteries whereby their efficiency in receiving blood from the ventricles is diminished and the brittleness of one's bones in old age are examples of this process. "*A man is as old as his arteries.*"

### Mental Growth

At birth the brain is relatively large, as is shown in Table LXIV of relative sizes of the various parts of the body at different ages.

Most of the tracts have their myelin sheaths, a notable exception being the cortico-spinal or pyramidal tracts which do not become myelinated until after birth.

The development of the nervous system depends upon receiving and analyzing afferent impulses, combining these with efferent impulses to form reflexes and finally to link all parts by a process of association. The human species differs from most lower animals in that it has fewer congenital responses, but has a greater capacity for education.

Although the new-born child does not show so many reflex responses as occur in some other animals we must remember that this does not prove that all the responses are acquired. It may be that the nervous system has not yet developed to the stage at which the inherited reflex patterns are fully formed.

An infant eight weeks old, when held under the armpits so that its feet could just touch the surface of a bed, was observed to place one foot in front of another. This was continued in a jerky hesitating manner by bringing the hindermost foot forward to place it in front of the other one. As the child could not crawl or stand it seems as if the stimulus of allowing the soles of its feet to touch a firm surface caused reflex stepping. At the same time the proprioceptive mechanism had not been sufficiently trained to produce anything more than a jerky uncertain alternate forward movement of the hindermost leg.

A good example of the process of training is seen in the eye movements. At birth an infant can see, as is evidenced by the movements of the eyes when a light is presented to it, but the eye movements are inco-ordinate and the eyes will not follow the light when it is moved. In three or four days time it will be found that the infant can now control its eyes sufficiently to follow a slowly moving object in a jerky irregular way.

A similar process of training is seen in the skeletal muscles. The inco-ordinate movements of the limbs are controlled as the pyramidal tract becomes myelinated. Gradually the child learns to crawl, stand and walk, wherein we see a gradual training of the muscles to respond to the afferent stimuli of muscle sense. The muscle sense is linked with the stimuli from the vestibule so that the child can balance and walk. Participation of cerebral control in these processes is shown by the inability to pay attention to anything else during the process and the inability to continue the walking for more than a few steps at a time. When the various parts have been trained to work together less cerebral control is required, and a child soon learns to walk and pay attention to other affairs at the same time. This seems to be an important rule that learning requires control by conscious effort, but that less and less

concentration is required as neural and muscular adjustments become more perfect. The individual who has learnt to play games when young more readily learns a new game than he who has had less neuro-muscular training.

Education in sensory reception and acquirement of discrimination between afferent impulses to produce perception seems to follow the same lines as neuro-muscular training. Afferent impulses which occur together become associated ; this is shown in the development of conditioned reflexes. In fact many of our so-called impulsive responses are due to conditioned reflexes whereby we respond to a stimulus in a manner which we would not expect until we trace the association between the stimulus and some other form of stimulus which has at one time of our life been associated with the actual stimulus received.

If it is possible to draw the line between physiology and experimental psychology it seems to be that the physiologist is mainly concerned with the response to a stimulus whilst the experimental psychologist is more interested in the response to the associations of the stimulus.

Thus we see that mental growth consists of a gradual training whereby the muscular movements are controlled, then a linking up of the nervous system so that skilled movements become possible. This latter is a correlation between muscles, sense organs and brain, which is especially produced by athletic sports, carpentry and other handicrafts.

Further integration leads to general ideas, and what one may term the thinking individual who associates apparently unlike events and weaves them into a consecutive whole, whereby a new hypothesis or even a theory may result.

Like physical growth mental growth reaches a maximum and then declines. It becomes more difficult to receive new ideas, but one still can deal with familiar ideas and make use of the accumulated material already acquired. Thus judgment becomes more marked than originality. This emphasizes the importance of a wide early education as it increases originality and improves one's judgment when one's originality is less in evidence. The wider one's interests the more one can deal with a diversity of subjects as one grows older. One becomes more efficient at those subjects that one knows, hence a wider experience leads to greater all-round efficiency.

With gradual waning of one's powers old age comes on. It may be a very gradual process, starting with decreased physical activity, then a lessened power of acquiring new ideas leading ultimately to recurrence to old familiar childhood associations.

### Death

The end of life is frequently premature before the gradual decline described above.

The falling off in rate of growth which ultimately leads to cessation of growth commences from the time of fertilization. Fertilization initiates development and the rate of growth is greatest at first. With the increase in size during development the amount of weight added in a given time may be greater, but the proportionate increase is less. The actual gain in growth shows a maximum when the product of size into rate of growth is maximum.

TABLE LXVII

RELATIVE INCREASE IN WEIGHT DURING INTRAUTERINE GROWTH (MINOT)

| Intrauterine Age (in months) | 1      | 2  | 3  | 4    | 5    | 6    | 7   | 8    | 9    |
|------------------------------|--------|----|----|------|------|------|-----|------|------|
| Relative Increase . . .      | 10,000 | 74 | 11 | 1.75 | 0.82 | 0.67 | 0.5 | 0.47 | 0.45 |

When death does occur it is due to failure of either the circulation, the respiration or the nervous system.

Respiration usually stops before the heart, but stopping of the heart will cause failure of the respiration because of the lack of blood to the respiratory centre. If the nervous system fails it is the respiratory centre which fails : in fact one may combine the nervous and respiratory failure into failure of the respiratory centres. The heart itself can continue independently of the nervous system. The cause of failure may be accident, such as haemorrhage, poisons such as those of disease or drugs, blocking of the respiratory passages, such as occurs in pneumonia, etc.

When death occurs the blood stagnates and becomes reduced, and rigor mortis ensues. *Rigor mortis* is a condition of coagulation of the muscles. It commences generally in a definite order. The stiffening commences in the jaw and neck, extends to the arms and finally reaches the legs. Conditions precedent to death affect the rapidity with which rigor mortis follows. Animals hunted to death show almost immediate rigor whilst wasting diseases are followed by slow development of rigor. The nervous system may have some influence on the rapidity with which it occurs.

After a certain period of rigor the muscles become soft again. This change may be the result of autolysis of the muscle tissue, or it may be a digestive change due to bacterial action. Further changes due to bacterial action resolve the tissues into simple compounds such as salts, water, carbon dioxide, ammonia, nitrogen, etc., thus returning to the air and soil those constituents which the plants have obtained during their growth.

Death is a relative condition. If the cerebrum of an animal is removed it will continue to breathe, yet it lacks sensation and

initiative : it has become a machine which gradually runs down. If the nervous system is cut off at a lower level, such as the junction of the medulla oblongata and spinal cord, respiration stops, but the animal may be kept going as a reflex machine if artificial respiration is supplied.

Isolated organs such as the mammalian heart, intestine, etc., may be kept active for some time if supplied with oxygen and kept warm and moist. The organs of cold-blooded animals remain active for a long time after removal from the body. For instance Mines kept frog's muscles alive and responsive to stimuli for twenty-one days.

Thus we see that death of the animal may be said to occur when the cerebrum is destroyed. Although the organism may exist as an automaton, it is not alive as a sentient being. That respiration and circulation may continue after death of the animal is a circumstance of great value as it enables one to study the mechanisms by which these systems carry out their functions. Isolated tissues, such as the heart or skeletal muscles, are also useful for the analysis of their properties.

The cycle of an individual existence commences with fertilization of the ovum and ends with death. It has been said that the Biological significance of death is that by removal of the older organisms room is made for newer ones. It is this replacement of old by new which provides for improvement in organisms by development of new characters.

NOTE.—For further information on some of the subjects discussed in Part IV, the student should consult W. M. Feldman, *Ante-Natal and Post-Natal Child Physiology* (Longmans, Green & Co.)



## APPENDIX

### METHODS FOR ELECTRICAL STIMULATION OF MUSCLE OR NERVE

In order to study living tissues by electrical stimulation one must be able to subject the part stimulated to any variation in strength, duration, periodicity or rate of change of current.

**Methods for Starting, Stopping or Varying the Strength of a Current.** A key may consist of a simple make and break key such as a Morse key. This consists of a strip of metal which can make contact with a piece of metal (Fig. 319). Instead of such a key a bent wire

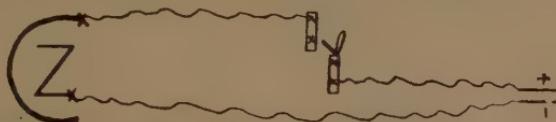


FIG. 319.—Plan of the Use of a simple Make and Break Key (Noël Paton).

may be dipped into mercury. By placing such a key in the course of a current the current can flow when contact is made, but not when the key is open.

A short-circuiting key is one which bridges a portion of the current. By closing the metal bar (Fig. 320) the current can flow across the bar, and the small amount that flows through the circuit beyond is

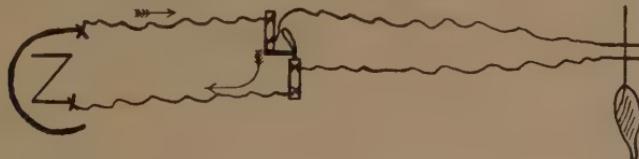


FIG. 320.—Plan of the Use of a Short-circuiting Key : shut (Noël Paton).

inversely proportional to the resistances of the key and of circuit respectively.

As the resistance of tissues is high and the resistance of the bar is very low, closing the key practically short-circuits the tissue, whilst opening the key causes the current to go through the tissue.

In order to vary the rate of change of current it is customary to use a liquid resistance and to vary the length of the column of liquid through which the current flows, or to vary the cross section through which the current can pass.

The former is usually accomplished by an annular groove containing salt solution. Two connections are made, one at each side of this groove. A rotating arm carries two metal strips which dip into the solution. When the rotating connections are close to the fixed ones the current is at a maximum, and when they are midway between the fixed contacts the current will be a minimum.

The second of these is exemplified by Keith Lucas' *Rheonome*. It consists of two compartments separated by a double wall pierced by a hole. Inside the double wall is a falling shutter with a Λ-shaped slot. As the shutter falls it cuts off the openings between the two compartments and therefore the current flowing through is reduced until the hole is completely closed. By raising the shutter the current can be increased as the opening is made wider. The speed of movement can be regulated, hence the rate of change of current can be regulated.

In the above description it is assumed that a constant current of uniform voltage, such as that from a galvanic cell or a storage battery, is being used. Such a current may be regarded as flowing from the positive to the negative pole. It is not unnecessary to describe the various forms of galvanic cells as they are described in any text-book of Physics.

#### METHODS FOR VARYING THE STRENGTH OF A CURRENT

##### A. Constant Current.

In order to vary the strength of a current, the resistance being uniform, we see that by the equation  $C = E/R$  we can alter the current by altering the electromotive force. This is accomplished by a potentiometer, sometimes called a rheocord (see Fig. 30, p. 42).

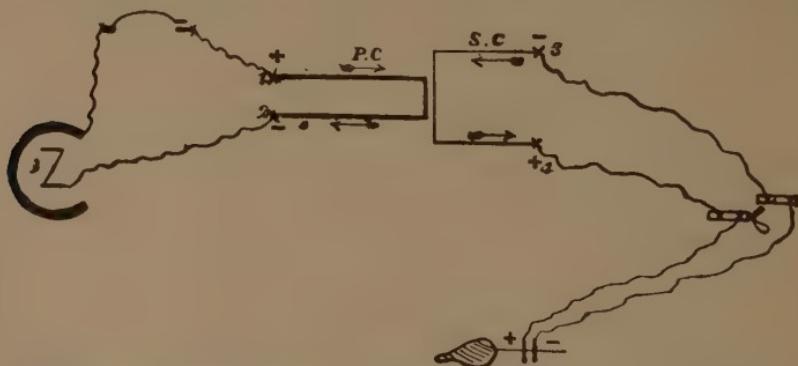


FIG. 321.—Diagram of an Induction Coil and its Connections.

P.C. = primary coil, S.C. = secondary coil. The arrows show the direction of the currents when contact is made in the primary circuit.

With a wire of uniform resistance per unit of length the fall of potential is proportional to the length of the wire. Thus with a wire one metre long and a difference of potential of one volt at the two ends, each millimetre will show a difference of potential of 0.001 volt.

By this means it is possible to use any desired electromotive force. In many instruments the wire instead of being straight may be arranged in a zig-zag or other pattern in order to economise space.

#### B. For Non-continuous Currents.

So far as physiology is concerned this means the use of an induction coil. The principle of this is that if a current is altered in a wire an induced current is produced in neighbouring wires (see Fig. 321). The current induced in each neighbouring wire is proportional to the rate of change of current in the inducing wire, inversely to (approximately the square of) the distance apart and to (the cosine of) the angle between the two wires. By winding the wires in coils a large number of turns of wire are brought together and the induced effect is roughly proportional to the number of turns in the inducing (primary) circuit to the number of turns in the induced (secondary) circuit. A complication is that each turn of the primary coil can exert an effect on the other turns. The induced effect is always of such a nature as to oppose the change which takes place in the inducing wire. Therefore when a current is started in the primary coil the current is opposed by an induced current in the opposite direction, hence it is slow in reaching its maximum value. On the other hand on stopping a current flowing in a primary coil the induced effect in the primary ought to continue the current so that it declines slowly. If the primary current is "broken" the original as well as the induced current is stopped, hence the current falls immediately from its full value to zero. For this reason the rate of change of current in the primary coil is greater at break than at make of the current, hence the induced current at break is greater than that at make.

If, however, the primary circuit is short circuited instead of broken, the induced current in the primary continues, the current falls off slowly and the induced current in the secondary coil is weaker, and more nearly of the magnitude of the induced current at make.

Various simple mechanical devices may be used so that the current in the primary coil may be made or broken synchronously with the movement of the surface on which the results of electrical stimulation are being recorded. Thus we can record the exact moment when the stimulation is applied to the tissue under observation.

The recording surface is provided with a projecting rod which hits the bar (*b*) of the key, causing the contact to be broken. If the recording surface is moved by hand with the muscle-nerve preparation writing on it, the position on the record which corresponds to the time of stimulation will be marked by the rise of the lever when the muscle contracts. Another way to mark the point of stimulation is to have a magnet in series with the key and arranged to record immediately under the recording point of the preparation. When the key is opened the lever of the magnet will indicate the time of stimulation.

When it is desired to stimulate by more than one stimulus we can use various mechanical devices for interrupting the primary coil. A vibrating spring dipping into mercury will give rhythmical stimuli of a definite rate, and this rate can be altered by changing the length of

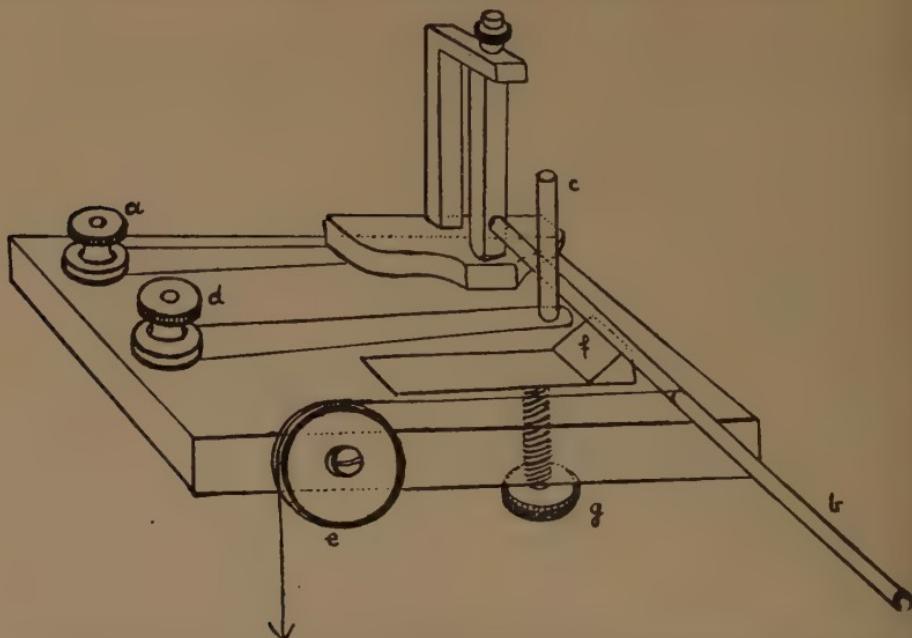


FIG. 322.—Diagram of Key for Stimulation by Break of the Primary Circuit (Roaf).

A striker on the drum by moving *b* away from *c* causes interruption of the current, the wedge *f* prevents *b* from being pulled back against *c*. When the key is to be used for more than one stimulus, the wedge *f* is moved out of the way by unscrewing *g*. The circuit is made through *a*, *c* and *b* to the striker on the drum. It is only when *c*, *b* and the drum are in contact that a current can flow, therefore there is a current of short duration each time a striker touches *b*.

the vibrating portion of the spring. For some purposes this vibrating spring does not continue to act for a long enough time, and it is there-

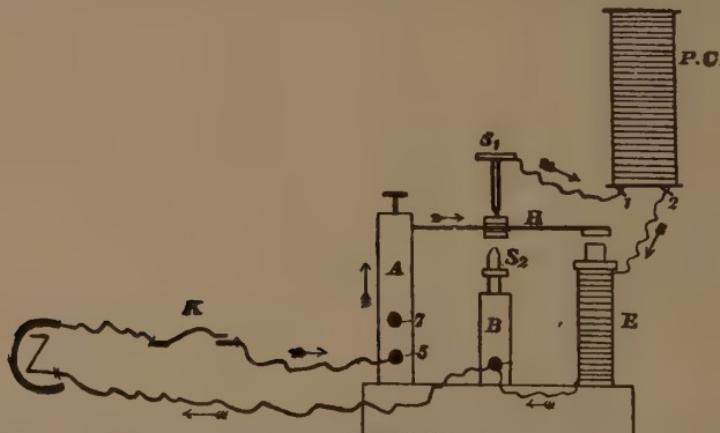


FIG. 323.—Diagram to show the Action of Wagner's Hammer. The arrows show the course of the primary current through the coil and magnet.

fore combined with a magnet whereby the current as it is made or broken attracts the spring at the proper phase of its movement, thus making it vibrate indefinitely. On most coils used for physiological

experiments the vibrating spring and magnet are part of the coil.

The arrangement for the vibrating hammer is that the current flows through the coils of a magnet at the same time that it flows through the primary coil. (The magnet may be the core of the primary coil.) The magnet attracts a bar of iron on the end of the spring H, which is in contact with a point on S, so that when the bar and spring are pulled on by the magnet there is a gap between the spring and point. As the spring and point are in series with the induction coil the current is broken when the magnet pulls the bar towards itself. The magnet now ceases to attract the bar, the spring flies back and contact is once more made. This make and break continues indefinitely and an induced current is produced at each make and break.

#### OTHER INSTRUMENTS FOR CONTROLLING THE CURRENT

If we wish to stimulate with the induction coil for a short interval of time a short circuiting key in the secondary circuit may be linked

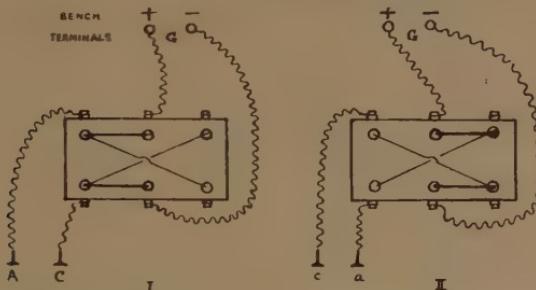


FIG. 324.—Diagram of Pohl's Commutator (Noël Paton).

I. Showing position of tilting contacts when current is flowing in one direction. II. When the direction of the current is reversed. The binding screws are connected to the mercury pools adjacent to them.

with the recording circuit just as the primary key was so linked for a single shock.

We may wish to pass the same current alternately through two circuits or to reverse the direction of the current. For the former we use a commutator and for the latter a reversing key. Pohl's commutator performs both these actions, but if one wishes to avoid the use of mercury the combined actions may be carried out by a key of the nature of that described by Smith and Roaf.

In the induction coils used for stimulation of muscle and nerve variation in the strength of the stimulation can be brought about:—

(1) By regulating the electromotive force of the inducing current, the make and break being as nearly instantaneous as possible.

(2) By varying the distance between the primary and secondary coils.

(3) By varying the angle between the two coils.

Alteration may also be produced by sliding the core into or out of

the primary coil or shielding the core, but the alterations by changing the core are rarely used.

In order to vary the distance between the coils the secondary is

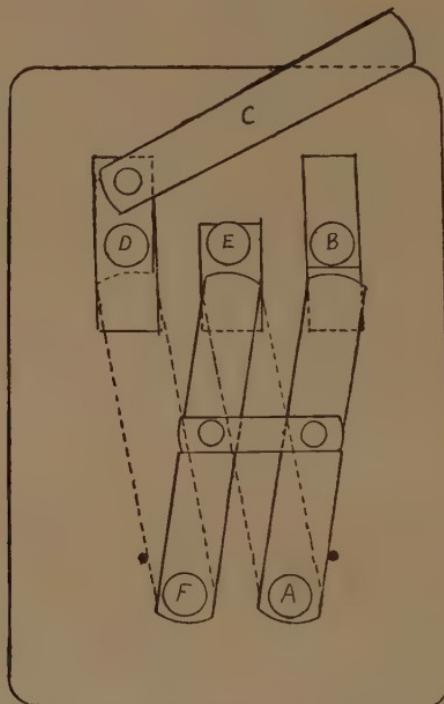


FIG. 325.—Diagram of Reversing Key and Commutator (Smith and Roaf).

With *C* open, two alternate circuits can be supplied. By sliding the contact bars to the position shown by the interrupted lines, the circuit *DE* will be completed instead of that of *EB*. By closing *C*, sliding the contact bars reverses the direction of a single current through the binding screws *E*, *B*.

constructed to slide away from the primary coil and frequently the secondary when removed from the primary can be rotated so that the current is reduced to zero when the two coils are at right angles to each other.

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